



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

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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-A<sub>2</sub> 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/IIIa 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 CANDAs). 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.

**NDA 20-718: Overall Index**

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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 <sup>a</sup>	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 <sup>1</sup>	X				X	X	X	X	X	X		
12 Lead ECG	X									X		
Hematology <sup>2</sup>	X									X	X	
Platelet Count <sup>3</sup>	X			X		X	X		X	X	X	
PT/aPTT <sup>4</sup>	X									X		
Serum Chemistry <sup>5</sup>	X									X		
CK/CK-MB	X					X	X		X	X		
Urinalysis <sup>6</sup>	X									X		
Angiographic Assessment	X		X									
Anti-Integrin Antibodies <sup>7</sup>	X										X	
Survey on Major Outcomes <sup>8</sup>										X	X	X
Infusion Start		X										
Platelet Aggregometry <sup>7</sup>	X	X		X		X						
Simplet Bleeding Time <sup>7,9</sup>	X	X <sup>9</sup>	X		X <sup>9</sup>							
Integrin Plasma Levels		X		X								

- <sup>a</sup> EOP = Immediately at end of angioplasty procedure.
- <sup>1</sup> Including blood pressure, pulse, respiration, and temperature.
- <sup>2</sup> Including hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count. CBC was also done when clinically significant bleeding occurred.
- <sup>3</sup> Platelet count was also done when clinically significant bleeding event occurred.
- <sup>4</sup> Also done when clinically significant bleeding occurred.
- <sup>5</sup> Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate.
- <sup>6</sup> Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood.
- <sup>7</sup> Testing was to be performed in 28 patients at Duke University and Cleveland Clinic.
- <sup>8</sup> Outcomes were assessed as they occurred or at discharge / 30 days / 6 months
- <sup>9</sup> Collection times were changed for Simplet 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 ( $\Delta$  in Hgb [or 1/3  $\Delta$  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	52	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				TOTAL
	Combined Integrilin	Combined Placebo	Integrilin 4 Hr	Integrilin 12 Hr	
Patients followed to hospital discharge [2 of 160 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	45	45	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	6	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 3.4).

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)
<b>Composite Endpoints at 6 Months</b>				
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	
	N=98	100%	N=46	100%
Number of Patients				
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	%
<b>TIMI CRITERIA</b>				
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
<b>INVESTIGATORS CRITERIA</b>				
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	6 (6%)	5 (11%)
Stent/Dextran required	1	2
Need for CABG	3	1
Could not Access Lesion	2	2
Discontinuations Due to Adverse Events	6 (6%)	1 (2%)
Bleeding or Drop in Hgb/Hct	5	0
Hypotension	1	0
Shock/Death	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)

Two patients in the 4-hour Integrilin-treated group discontinued for reasons other than angioplasty failure or adverse events.

**Laboratory Adverse Events:** No notable differences in mean Hgb reduction between any of the study arms were observed (e.g., the mean baseline Hgb of 14.1 g/dL decreased to 12.9 g/dL in the combined Integrilin-treated group, compared to a mean baseline of 14.0 g/dL that decreased to 12.8 g/dL in the combined placebo-treated group). These decreases had returned to baseline by the 30-day assessment.

Calculation of the mean nadir Hgb or Hct values for each group revealed no differences. The bleeding index, a value that approximates the concentration of Hgb lost due to bleeding, was greater in the combined Integrilin group (2.3 g/dL) than in the combined placebo group (1.9 g/dL).

The mean platelet counts decreased slightly post-procedure in both the Integrilin and placebo combined treatment groups. One patient in the 4-hour Integrilin-treated group developed new onset thrombocytopenia to 48,000/cmm after CABG surgery. Two other Integrilin-treated patients developed nadir platelet counts of 98,000/cmm and 99,000/cmm that reversed spontaneously.

No clinically meaningful trends were observed in the mean values for the serum electrolytes, glucose, or renal indices. Only two patients had SGOT that were 3 X ULN. Both of these patients had normal baseline values that were increased significantly at discharge.

There was only one patient with a marked elevation in creatinine (greater than 1.5 times ULN), possibly due to acute tubular necrosis secondary to the contrast media. The creatinine decreased to 2.3 mg/dL five days later.

The mean prothrombin time (PT) was similar between treatment groups at baseline and discharge. Three patients were noted to have a prolonged PT at discharge who were not on concomitant warfarin therapy; two in the Integrilin group and one in the placebo group.

Analysis of the mean aPTT revealed elevated (greater than 1.5 times control) values at baseline consistent with the fact that many patients entered the study on concomitant heparin. The aPTT values had returned to normal at discharge. No meaningful differences between the study groups were observed.

## CONCLUSIONS

Two regimens of Integrilin were compared to placebo in 144 patients undergoing PTCA. The study was primarily designed for PK/PD and safety evaluations in order to plan for the a phase III study, with only a preliminary assessment of efficacy.

Integrilin reduced the incidence of the composite endpoint of death, MI, or urgent intervention at 30 days after PTCA to 6.9% compared to that of 12.2% for placebo. A dose-dependent effect was observed as patients receiving the longer infusion (12 hrs) exhibited a lower incidence of the primary endpoint than those receiving the shorter (4 hr infusion): 4.1% versus 9.6%, respectively. However, the small study size precluded statistical analysis of the event rate difference.

Patients receiving Integrilin experienced a higher incidence of bleeding events (44.9% vs 19.6%), a higher incidence of transfusions (8.2% vs. 4.3%), and had higher mean bleeding index (mean of 2.3 vs. 1.9) than placebo-treated patients. The majority of bleeding events experienced by Integrilin patients were not severe. Major bleeding, as defined by either a >5 g/dL loss in Hgb or intracranial bleeding (the TIMI criteria), was not increased in Integrilin patients compared to placebo patients: 5.1% vs. 8.7% in the Integrilin and placebo groups, respectively. No increased incidence of bleeding was observed in patients who received the 12 hr infusion of Integrilin compared to the 4 hr infusion.

Plasma levels of Integrilin, Simplate bleeding time, *ex vivo* platelet aggregation and serum antibodies to Integrilin were assessed in a subset of patients. Only two plasma levels were obtained from each of 24 patients precluding a formal PK analysis. Simplate bleeding time was prolonged by approximately 2 to 4-fold during the Integrilin infusion and returned toward baseline following the infusion. Platelet aggregation was less than 20% of baseline in nearly all patients in whom it was assessed during both infusions and returned rapidly toward baseline following the infusion. The data did not permit a formal PD analysis and estimate of IC 50. Serum antibodies to Integrilin were not detected in any of the 22 patients in whom they were assessed.

In conclusion, the incidence of composite endpoint was lower in the Integrilin groups compared to placebo at 30 days, however, the study was not designed for efficacy analysis. At 6 months there was no difference among groups, rather there was a higher rates of non-urgent revascularizations in the Integrilin groups. More bleeding occurred in the Integrilin group. Although severe bleeding was not reported more frequently in the treated than in the placebo group, treated patients required more transfusions.

No dose relationship was observed for bleeding in the two Integrilin groups.

**Study 93-012/ IMPACT High-Low (NDA Vol. 1.105 - 1.108)**

This was a Phase II randomized, placebo-controlled, multi-center investigation in patients with coronary artery disease (CAD) undergoing percutaneous transluminal coronary angioplasty (PTCA) with an FDA approved device (balloon catheter, directional atherectomy transluminal extraction catheter, or excimer laser).

The objectives of the clinical study were:

- to evaluate the PK/PD of various dosing regimens of Integrilin in PTCA patients;
- to determine the acute effects on hemostasis of various doses of Integrilin combined with heparin; and
- to evaluate the safety of Integrilin in patients undergoing coronary angioplasty.

The primary PK/PD study endpoints were determining by Integrilin plasma levels, inhibition of *ex vivo* platelet aggregation/agglutination, and Simplate bleeding time.

The safety of Integrilin was evaluated by the incidence of clinical outcomes, adverse events and bleeding events, clinical laboratory, and physical findings.

Clinical efficacy was evaluated by the composite endpoint of death, MI, repeated coronary intervention within 24 hours after study drug infusion.

**Study Population:** Patients with the diagnosis of coronary artery disease documented by cardiac catheterization and scheduled for coronary angioplasty were eligible for the study.

The inclusion and exclusion criteria and the criteria for withdrawal from the study or discontinuation were similar to those described for study 92-009 (IMPACT I).

No formal sample size or power calculation were performed in this study.

Approximately six patients per group were needed for reliable determination of drug effect on platelet aggregation and bleeding time.

**Treatments:** The dosing regimens selected for the study were based on the results of previous studies. The two initial regimens (for study groups A and C) were chosen on the basis of PK modeling that fit a bolus to a high and low dose infusion. Subsequent regimens were chosen to attempt to optimize inhibition of platelet aggregation both immediately and over the course of the infusion.

Originally, six patients were scheduled for each of three dose groups, for a total of 18 patients, with additional dose groups to be added upon analysis of platelet function data in these initial groups.

Integrilin (lot # C0007A) and placebo were provided by COR Therapeutics, Inc. Concomitant therapy was used as clinically indicated.

A total of 73 patients were ultimately randomized to either integrilin or placebo at four study sites. The dosing regimens studied, and concomitant therapy are summarized in Table 3-2.

Table 3-2: Dosing Regimens and Use of Concomitant Medications

Dose Group	Ratio: Integrilin/ placebo	Blind Status	Bolus Dose (ug/kg)	Infusion Rate (ug/kg/min)	Infusion Duration	Heparin Regimen	ASA Regimen
A n=6	2:1	D/B	180	1.00	18-24 hours	Before and during PTCA: 140 ug/kg bolus iv, then infusion to maintain ACT > 300-500".  Post-PTCA: 15 ug/kg-hr iv to maintain APTT 2-2.5 x control	325 mg (qd)
C n=6	2:1	D/B	135	0.50			
D n=9	2:1	D/B	90	0.75			
E n=10	2:1	D/B	135	0.75			
n=26	3:1	O/L	135	0.75			
	3:1	O/L	135	0.50			
G n=16	3:1	O/L	135	0.50			

Dose group B was eliminated in Protocol Amendment I. Dosage Groups F and G were added in order to gain additional safety data on the two dosage regimens that had been chosen to be included in the Phase III study.

Patients were enrolled consecutively into sequential dose groups and then randomly assigned to receive either Integrilin or placebo by intravenous bolus dose begun 30 minutes prior to the start of the angioplasty procedure, followed by continuous IV infusion of 18-24 hours duration from the end of the coronary angioplasty procedure. The regimen was based on the results of the EPIC study which indicated that a bolus and continuous infusion of 12 hours of abciximab was effective, whereas a bolus dose alone was not effective in this indication.

For the analysis, data on all placebo patients, irrespective of dose group, were combined. For patients receiving Integrilin, the data of dose groups receiving the same regimens (C and G, E and F) were also combined. For each analysis, the effects of various Integrilin dosing regimens and placebo were compared.

### ASSESSMENT OF PHARMACODYNAMICS AND PHARMACOKINETICS

Platelet Aggregation: Platelet aggregometry was performed using two agonists: ADP 20 uM and ristocetin. Ristocetin co-factor was also determined. Platelet aggregation/agglutination was determined at pre-infusion; 0.25, 0.5, 1, and 2 hours after the start of infusion; infusion termination; and 2 and 4 hours post-infusion.

Bleeding Time: Simplate bleeding time was performed at pre-infusion; 30 minutes prior to infusion termination; and 1 hour post-infusion. Bleeding times of more than 30 minutes were truncated.

Pharmacokinetics: Plasma samples were drawn at 0.25, 0.5, 1, 2, 4, and 12 hours after the initiation of infusion; infusion termination; and 0.25, 0.5, 1, 2, 4, 8, and 12 hours post-infusion.

### EVALUATION OF CLINICAL OUTCOME AND SAFETY

Clinical Outcomes: Data on specific clinical or procedural outcomes, including death, myocardial infarction (MI), repeat catheterization, repeat coronary angioplasty, CABG, bleeding, stroke, recurrent ischemia, reocclusion, congestive heart failure/pulmonary edema, and cardiogenic shock, were collected through 24 hours post-infusion.

Adverse Events and Bleeding Complications: All adverse events occurring between randomization and 24 hours post-infusion were recorded in the CRF. Bleeding events were captured separately in the CRF. The severity of bleeding events was described in two ways: 1) as mild, moderate, or severe (as stated on the CRF); and, 2) as major or minor according to the TIMI criteria. The CRF definitions of bleeding severity, as assessed by the investigator, and the TIMI classification of bleeding were as described for study 92-009 (IMPACT I). For patients who were transfused prior to a determination of major or minor bleeding, the loss in Hgb due to bleeding was calculated by the bleeding index.

Disposition of Patients: Four of the 73 randomized patients were not treated. One patient from Group F experienced bleeding prior to treatment with study drug. Two placebo patients from Group D were not treated by investigators' decision. One patient from Group G was not treated because the characteristics of the coronary artery lesion prevented angioplasty. Eight additional patients (seven Integrilin, one placebo) had study drug terminated early. One placebo patient was terminated due to need for other procedure; one patient in group D was terminated because the PTCA was not performed; two

patients in group C & G were terminated because of bleeding or drop in Hgb/Hct; four patients in group E & F were terminated due to bleeding (2 patients), inability to cross lesion (1 patient), and use of rotablator (1 patient).

Protocol Deviations: Twenty-one of the 73 (28.8%) randomized patients did not meet all eligibility criteria. Eight patients were enrolled who had a history of CVA, 7 had a baseline PT of more than 16.2 and/or were on warfarin, 2 had no angioplasty procedure information reported, 1 had no stenotic lesions and maximum stenosis of less than the required 60%, 1 had no lesions treated by coronary angioplasty due to 100% occlusion of the graft site, 2 patients had a prior coronary angioplasty performed within 6 weeks of study participation.

Demographics, medical history and angiographic data: There were no major differences among groups for demographic or baseline characteristics. A total of 94 lesions were treated among 71 patients. The majority of patients (67/71; 94.4%) were treated with standard balloon angioplasty. The overall mean percent stenosis pre-coronary angioplasty was  $83.8 \pm 9.84$ . The post-coronary angioplasty percent stenosis was  $21.7 \pm 17.24$ . Four lesions, two in the Integrilin 135/0.75 dose group and one each in the combined placebo and Integrilin 135/0.5 dose groups, had greater than 50% stenosis post-coronary angioplasty. Failure to cross the lesion (two lesions) and failure to dilate the lesion (one lesion) were the two reasons given for the failures; one failure was due to an abrupt closure. The mean pre-coronary angioplasty diagnostic catheterization value for ejection fraction, reported in 53 patients, was  $53.7 \pm 10.89\%$ .

Dissection occurred in 22 lesions, three (3/94; 3.2%) of which were considered to be major dissections. The highest dose group incurred no dissections; minor dissections occurred in all other dose groups. Possible thrombus was noted in eight lesions post-angioplasty: 5 in the 135/0.75 dose group, two in the 135/0.5 dose group, and one in the combined placebo group.

Concomitant medications: The median dose of heparin during the procedure was higher in the control group than in the Integrilin groups. The total dose of post-procedural heparin was similar in the control and Integrilin-treated groups. A total of 67/73 (91.8%) patients received Aspirin prior to study drug.

The majority of patients received nitrates or calcium channel blockers. Almost half the randomized patients had received beta blockers or heparin. Post-procedure, aspirin was the most commonly administered concomitant medication and one third (34.2%) of the patients were on aspirin at discharge.

## STUDY RESULTS

### Pharmacodynamic and Pharmacokinetic Data

Platelet Aggregation and Agglutination: Inhibition of ADP-induced platelet aggregation in each treatment group was expressed as percent of baseline. The following parameters were determined for each subject based on visual inspection of the data:

$PA_{min}$  = Minimum value of the platelet aggregation as a percent (%) of the baseline value

$T_{min}$  = Time of occurrence for  $PA_{min}$

The maximum change from baseline as percent of baseline ( $PA_{min}$ ) for individual patients and the means for each Integrilin dose and placebo are summarized below

Table 5-1 Maximum Change from Baseline in Platelet Aggregation as a Percent of Baseline

	Placebo	Integrilin 90/0.75	Integrilin 135/0.5	Integrilin 135/0.75	Integrilin 180/1.0
N	6	5	14	25	4
Mean	88	15	6.0	4.4	1.9
S.D.	13	9.2	5.9	4.2	2.3

In all Integrilin groups, platelet aggregation was below 20% of baseline at the first time point of evaluation (15 minutes) and throughout the infusion.

The mean effect was greatest at the highest infusion rate of 1.0 ug/kg-min and there was a suggestion of a dose-effect relationship.

Platelet aggregation returned toward baseline following termination of the infusion.

An estimate of the IC 50 and the IC 80 (the plasma level of Integrilin associated with a 50% and 80% inhibition of *ex vivo* platelet aggregation) in the patients scheduled for angioplasty was evaluated using a generalized logistic-logarithmic regression model. The resulting estimates were 93 ng/mL and 292 ng/mL for the IC 50 and the IC 80, respectively and significantly higher than those observed in normal volunteers where the estimated IC 50 ranged from 38 to 55 ng/mL and the IC 80 from 100 to 175 ng/mL.

The data on the effect of integrilin on *ex vivo* platelet agglutination by ristocitin were insufficient, but it appeared that the inhibitory effect of Integrilin was less consistent and less profound in this assay.

**Bleeding Time:** The following parameters were determined for each subject:

$BT_{max}$  = Maximum value of Simplate bleeding time after the start of the infusion expressed as a ratio of the baseline value

$T_{max}$  = The time associated with the observed  $BT_{max}$

A summary of the mean effect on bleeding time for each of the Integrilin infusion groups and placebo expressed as a ratio of the baseline value is shown in Table 5-4.

Table 5-4 Mean Effect on Bleeding Time (min) by Treatment Group  
(Expressed as maximum Change from Baseline)

	Placebo	Integrilin 90/0.75	Integrilin 135/0.5	Integrilin 135/0.75	Integrilin 180/1.0
N	8	4	15	24	3
Mean	1.58	1.66	2.36	2.59	3.68
SD	0.78	0.53	1.05	1.08	0.28

The overall mean bleeding time was 8 min. in all treatment groups. Prior to infusion termination, the mean bleeding time increased with increasing Integrilin dose; from 8' in the placebo group to 21' in the highest Integrilin dose group with a dose effect relationship. Bleeding time were nearly at baseline one hour after terminating the infusion.

Multiple measurements of plasma levels of Integrilin were obtained in 51 patients. The resulting overall estimate of the PK parameters were consistent with a plasma clearance of 142 mL/kg-hr, a volume of distribution at steady state of 456 mL/kg and a plasma elimination half-life of 2.21 hr. The estimates of steady state plasma concentrations of Integrilin associated with the infusion rates of 0.5, 0.75 and 1.0 ug/kg-min were 254, 336 and 458 ng/mL, respectively.

The estimated plasma clearance of Integrilin in this population of elderly patients with ischemic heart disease was lower than that observed in younger, normal volunteers (range of 223-363 mL/kg-hr) and consistent with the lower plasma clearance observed in earlier PK study in patients with ischemic heart disease. Similarly, the plasma elimination half-life of the study population was somewhat longer than the 0.5-1.14 hr observed in young, normal volunteers.

#### Clinical Endpoints: Efficacy/Safety Evaluations

The incidence of clinical endpoints, namely ischemic events, are presented for all 73 randomized patients.

The analyses of adverse events, laboratory data, vital signs and physical examination findings include the 69 patients treated with study drug.

**Clinical Endpoints: Ischemic Events:** Five patients, two treated with placebo and three with Integrilin, experienced recurrent coronary ischemia; three of whom were assessed as having MI. Four patients, three placebo and one 135/0.5 Integrilin, underwent repeat catheterization. Two of these patients, both in the combined placebo group, also underwent repeat PTCA; one of these coronary angioplasty procedures was an emergency. One placebo patient, who failed coronary angioplasty, discontinued study medication infusion to undergo emergency CABG. The placebo patient also experienced cardiogenic shock and CHF.

In addition to these ischemic events reported as clinical endpoints, there were four patients who reported angina pectoris as adverse events through 24 hours post-infusion. Two of these patients were in the 135/0.5 Integrilin dose group, one was in the 135/0.75 dose group, and one was in the placebo group.

A post-hoc analysis of the composite endpoint of MI and urgent revascularization (no deaths occurred in this study) over 24 hours post-infusion was done for comparison with other Phase II studies and IMPACT II study. Three patients in the placebo group and one patient in the 135/0.5 Integrilin group experienced composite endpoint through 24 hours post-infusion.

Overall, clinical events were more common in the combined placebo group than in the Integrilin-treated patients.

**Adverse Events: Deaths and Discontinuations Due to Adverse Events:** No patients died. Five patients prematurely discontinued study drug due to an adverse event: one patient who received placebo, and two each who received Integrilin 135/0.5 and Integrilin 135/0.75. The placebo patient failed coronary angioplasty and discontinued study medication to undergo emergency CABG. The remaining patients discontinued Integrilin primarily because of bleeding (GI and groin bleed). All of these patients had their study drug unblinded.

**Serious Adverse Events:** A total of 14 patients experienced serious adverse events. Five of these 14 patients experienced an ischemic event (clinical endpoints). Two patients experienced major bleeds. Two patients experienced both an ischemic event and a major bleed. Five patients, one of whom was placebo-treated, experienced a serious adverse event other than an ischemic event or major bleed. One placebo-treated patient and three patients in the 135/0.75 dose group experienced hypotension.

Clinical information for these 14 patients is summarized in Table 6-4.

**Table 6-4**  
Patients with Serious Adverse Events

Treatment Group	Patient Number	Gender, Age (yr)	Event (COSTART Preferred Term)	Indicator (s) of Seriousness
Combined Placebo	01003	Male, 51	Accelerated Idioventricular rhythm (BRADYCARDIA) at 24.5 hr post-infusion termination	Action = Temporary pacemaker, repeat cath/angioplasty
	01007	Male, 46	Myocardial infarction, recurrent ischemia, reocclusion (CORONARY OCCLUSION) within 24 hr post-infusion	Severity = severe; action = repeat cath/angio
	01010	Male, 64	Abrupt closure with several complications (CORONARY REOCCLUSION, MI, RESP FAIL) within 24 hr post-infusion	Severity = severe; action = IABP, fluids, antibiotics, ventilator required, repeat cath/angio. (Also classified as having major bleed.)
	01018	Female, 46	Abrupt closure; CABG requiring study drug discontinuation	Major bleed
	02021	Male, 48	Hypotension	Action = IV fluids
90 µg/kg + 0.75 µg/kg-min	01008	Male, 46	Mild infection (INFECT) 15 min prior to infusion termination	Fever, elevated WBC Action = cultures/antibiotics
135 µg/kg + 0.5 µg/kg-min	03006	Male, 70	Recurrent ischemia within 24 hr post-infusion	Severity = severe; action = repeat cath/angio
	04008	Female, 60	Recurrent ischemia, myocardial infarction (INFARCT MYOCARD) within 24 hr post-infusion	Severity = severe
135 µg/kg + 0.75 µg/kg-min	01013	Male, 69	Hematoma requiring transfusion	Major bleed
	02013	Male, 60	Hypotension (HYPOTENS) while on pressors during study drug infusion	Action = dopamine increased
	02017	Male, 63	Hypotension (HYPOTENS) while on pressors during study drug infusion	Action = dopamine, fluids
	02020	Male, 61	Hypotension (HYPOTENS) and bradycardia within 24 hr post-infusion	Action = atropine, IV fluids
	03005	Male, 70	Recurrent ischemia (ISCHEMIA MYOCARD) within 24 hr post-infusion	Severity = severe
180 µg/kg + 1.0 µg/kg-min	01001	Male, 71	GI bleed requiring transfusion (HEM)	Major bleed; action = colonoscopy/biopsy

[Source: Summary Listings 20, 22, 23, 24, 25, 26, 27, 28]

**Bleeding Events:** Patients were classified according to the TIMI criteria as having major, minor, or insignificant bleeding. Changes in hemoglobin and hematocrit were taken as the change from baseline to the lowest reported values; hemoglobin changes were adjusted for transfusions. In addition, individual bleeding events were classified by the investigator as mild, moderate, or severe.

Reported bleeding events by treatment group are summarized in Table 6-5.

**Table 6-5**  
Summary of Bleeding Events for Treated Patients by Treatment Group

Bleeding Measure	Combined Placebo (N=17)		Integrelin 90 µg/kg + 0.75 µg/kg-min (N=5)		Integrelin 135 µg/kg + 0.5 µg/kg-min (N=16)		Integrelin 135 µg/kg + 0.75 µg/kg-min (N=27)		Integrelin 180 µg/kg + 1.0 µg/kg-min (N=4)	
	N	%	N	%	N	%	N	%	N	%
<b>Bleeding Classification</b>										
None	8	47.1	0	0.0	7	43.8	8	29.6	1	25.0
Insignificant	5	29.4	4	80.0	3	18.8	13	48.1	1	25.0
Minor	2	11.8	1	20.0	6	37.5	5	18.5	1	25.0
Major	2	11.8	0	0.0	0	0.0	1	3.7	1	25.0
<b>Number of Bleeding Events within 24 hr Post-Infusion</b>										
0	10	58.8	1	20.0	10	62.5	11	40.7	1	25.0
1	6	35.3	3	60.0	5	31.1	13	48.1	1	25.0
2	1	5.9	1	20.0	1	6.3	3	11.1	1	25.0
3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
4	0	0.0	0	0.0	0	0.0	0	0.0	1	25.0
<b>Bleeding Severity</b>										
Mild	8	100.0	5	100.0	7	100.0	18	94.7	6	85.7
Moderate	0		0		0		1	5.3	1	14.3
Severe	0		0		0		0	0.0	0	0.0
Total Events	8		5		7		19		7	

A total of 46 events were reported for 36 (52.2%) patients either during infusion or within 24 hours post-infusion. None of these 46 events was severe; all but two, one in each of the highest dose groups, were mild.

Changes in Hgb/Hct were used to identify major or minor bleeds according to the TIMI criteria. Five of the 69 treated patients were categorized as having minor or major bleeding based only on Hgb/Hct changes. Twenty-eight (40.6%) patients who reported a bleeding event had insignificant bleeding based on Hgb/Hct changes; 15 (21.7%) had minor bleeding. Four (5.8%) patients, two placebo-treated and two Integrilin-treated (135/0.75 and 180/1.0) had major bleeding defined by changes in Hgb/Hct. There were no intracranial bleeds reported.

Transfusions: Two patients received transfusions, one in each of the highest Integrilin dose groups. These patients had major bleeds.

Non-bleeding Adverse Events: A total of 118 adverse events were reported, including clinical endpoints (i.e., ischemic events), by 69 patients. Six of these events occurred prior to study drug, and 43 occurred more than 24 hours post-infusion. A total of 69 events were reported for 59 patients through 24 hours post-infusion. The most frequently reported (5% or more) non-bleeding adverse events are summarized by the COSTART preferred term in Table 6-8.

**Table 6-8**  
Nonbleeding Adverse Events Reported by 5% or More of Treated Patients Through 24 Hours Post-Infusion

Body System	COSTART Preferred Term	Combined Placebo N=17		Integrilin 90 µg/kg + 0.75 µg/kg-min N=5		Integrilin 135 µg/kg + 0.5 µg/kg-min N=16		Integrilin 135 µg/kg + 0.75 µg/kg-min N=27		Integrilin 180 µg/kg + 1.0 µg/kg-min N=4	
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Body as a Whole	Back Pain	11	(64.7)	2	(40.0)	10	(62.5)	11	(40.7)	1	(25.0)
	Headache	1	(5.9)	1	(20.0)	2	(12.5)	4	(14.8)	0	
	Pain	1	(5.9)	0		2	(12.5)	2	(7.4)	0	
	Infection	1	(5.9)	0		0		0		0	
	Pelvic Pain	0		0		2	(12.5)	3	(11.1)	0	
	Abdominal Pain	0		1	(20.0)	1	(6.3)	0		1	(25.0)
Cardiovascular System	Hypotension	3	(17.6)	0		3	(18.8)	6	(22.2)	0	
	Angina Pectoris	1	(5.9)	0		1	(6.3)	1	(3.7)	0	
	Coronary Artery Disorder	1	(5.9)	0		0		0		0	
Digestive System	Nausea	3	(17.6)	2	(40.0)	3	(18.8)	6	(22.2)	2	(50.0)
	Vomiting	0		0	(20.0)	1	(6.3)	3	(11.1)	1	(25.0)

### Laboratory Data

Hematology: Overall, 48.4% (31/64) of treated patients with normal Hgb values pre-infusion experienced a decrease at infusion termination; the remaining 33 (51.6%) patients had values that did not change from normal range.

No trends were noted with increasing Integrilin dose.

The minimum reported nadir Hct decreased with increasing Integrilin dose from 31.9% in the lowest dose group to 22.0% in the highest dose group; the lowest reported nadir Hct (18.0%) was in a placebo patient.

No significant or clinically relevant changes in WBC or platelet counts occurred during the study. Results for other blood counts (red blood cell count, differential counts) were unremarkable.

Coagulation Tests (aPTT and PT): The changes in aPTT and PT were compatible with heparinization for coronary angioplasty.

Serum Chemistry: Many patients had missing values at 24 hours post-infusion. Four patients, two placebo- and two Integrilin-treated, with normal pre-infusion SGOT had abnormally high values at infusion termination. One of the patients with high values, treated with Integrilin 135/0.5, had an MI and multiple episodes of recurrent ischemia during Integrilin infusion.

The majority (64.9%; 37/69) of treated patients had normal SGPT values at both pre-infusion and infusion termination.

Results for alkaline phosphatase were similar. Two patients, one placebo and one Integrilin-treated patient, had increase in LDH at infusion termination.

No clinically significant changes occurred for serum creatinine and electrolytes.

Urinalysis: Fifteen (31.3%) patients, two treated with placebo and 13 with Integrilin, had positive occult blood after study drug administration.

Cardiac Enzymes (CK and CK-MB): CK and CK-MB were collected at various times. CK-MB levels were available for only 41 patients, and CK-MB as a percentage of CK were available for only 17 patients at pre-infusion.

Six patients, three placebo and three integrilin, had increased levels of CK and CK-MB. Four of the six patients (two placebo and two integrilin-treated) experienced clinical outcome.

### CONCLUSIONS

This was a PK/PD study of Integrilin in a population of patients with ischemic heart disease scheduled for PTCA. The objective of the study was to identify the dosage groups that would be included in the pivotal Phase III study based on the PK, PD and safety parameters.

A total of 51 patients had multiple measurements of plasma Integrilin concentrations during and following their infusions. A dose-related effect was observed on Simplate bleeding time during the infusion. At all dose levels, the bleeding time returned toward baseline one hour after terminating the infusion.

The effect on *ex vivo* ADP-induced platelet aggregation during the infusion was observed at all dose levels. The effect was rapid with >80% inhibition of platelet aggregation which promptly returned toward baseline values after the infusion. The IC 50 and the IC 80 were significantly higher than those observed in normal volunteers.

The incidence of ischemic complications was suggestive of an anti-thrombotic effect of integrilin, however, the study was not designed for efficacy evaluation.

Study drug was discontinued early in one placebo and four Integrilin-treated patients due to adverse events.

A total of 14 patients, five placebo and nine Integrilin-treated, experienced serious adverse events. There were no deaths. There were 5 ischemic events, 2 major bleeds, 2 both ischemic event and a major bleed, 1 infection and 4 hypotension.

Two placebo and two Integrilin patients experienced major bleeding events.

Based on the results of the study, the bolus dose selected for the Phase III study was 135 ug/kg since it optimally inhibited platelet aggregation during angioplasty. Continuous infusion of 0.75 ug/kg-min and 0.5 ug/kg-min for 18-24 hours were selected as they adequately sustained the platelet aggregation inhibition with acceptable peri-procedure safety and post-procedure efficacy.

**PROTOCOL 93-014/IMPACT II** (NDA Vol. 109-195)

**Study Title:** A Randomized, Double-Blind Efficacy and Safety Evaluation of Two Dosing Regimens of Integrilin versus Placebo for Reducing the Complications of Coronary Angioplasty (The IMPACT II Study)

IMPACT II study is the pivotal study in NDA 20-718 and provides 94.7% of the total patients database in the NDA.

**INVESTIGATIONAL PLAN**

The IMPACT II study is a Phase III multi-center, double-blind, randomized, placebo-controlled clinical study of patients undergoing coronary angioplasty (balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty or excimer laser angioplasty [PTCA]).

**Study Objectives:** Primary objectives of the study were:

- To compare the efficacy of two Integrilin dosing regimens with the effect of placebo in reducing ischemic complications of coronary angioplasty. Clinical efficacy was evaluated with a composite endpoint comprising death, MI (including infarction extension or reinfarction) and urgent or emergency coronary revascularization (coronary angioplasty, coronary artery bypass graft surgery, or stent placement for abrupt closure).
- To determine the safety profiles of two dosing regimens of Integrilin compared to placebo.

**Study Treatments:** Three treatment regimens, each incorporating a bolus dose followed by a continuous infusion lasting 20-24 hours were compared

- 135 ug/kg bolus followed by a continuous infusion of Integrilin (0.5 ug/kg-min) (the low dose group);
- 135 ug/kg bolus of Integrilin followed by a higher continuous infusion (0.75 ug/kg-min) for 20-24 hours (the high dose group); or
- a matching placebo bolus followed by a matching placebo infusion.

The dosing regimens of integrilin (bolus and infusion) were chosen based on the safety data and on the pharmacodynamic results of study 93-012 (the IMPACT High/Low study) to produce a prompt and sustained inhibition of platelet aggregation. The bolus dose of 135 ug/kg of Integrilin was chosen for both Integrilin-treated groups in the IMPACT II study since that dose provided an effective level of inhibition of platelet aggregation during coronary angioplasty

when maximal antithrombotic activity is required. The duration of infusion of 20-24 hours was determined by the results of the EPIC study where a bolus administration of abciximab (a murine antibody to GPIIb/IIIa) followed by a 12 hour infusion was more effective than the bolus dose alone regimen. Lower infusion doses of 0.5 mg/kg-min and 0.75 mg/kg-min were selected to minimize the risk of bleeding which had been observed in the EPIC study.

All patients received aspirin (325 mg) within 24 hours prior to PTCA and an intravenous (IV) heparin bolus of 100 units/kg followed by up to 2000 additional units as a bolus injection every 15 minutes to maintain an ACT between 300-350 seconds. Heparin infusion was continued after the coronary procedure to maintain a therapeutic elevation of the activated partial thromboplastin time (aPTT) of 2-3 times control. After sheath removal, heparin was continued or discontinued at the Investigator's discretion.

The use of other concomitant medications was left to the Investigator's discretion. Intravenous thrombolytic therapy was not administered during study drug administration, although intra coronary thrombolytic therapy was permitted in emergency circumstances and guidelines for its administration were provided.

Investigators had the option of using a "stent kit" for patients in whom a stent was placed. This procedure allowed the use of a blinded vial of Dextran-40 or a matching placebo. The stent kit randomization was linked to the original randomization so patients receiving Integrilin were randomized to placebo Dextran and patients receiving placebo were randomized to Dextran. Patients who were to receive open-label Dextran-40 in conjunction with intra coronary stent placement were to discontinue the study drug infusion due to the potentially high risk of bleeding with the concomitant administration of Dextran-40 and Integrilin.

Patients were followed until hospital discharge and were re-evaluated at 30 days following randomization. A long-term evaluation for efficacy was performed 6 months post-randomization.

Study Procedures and Flow Chart: All patients had clinical and laboratory baseline and periodic evaluations including ECG and angiographic tests.

Subpopulation of patients were studied for development of anti-Integrilin antibodies, Pharmacokinetics and Mass Balance.

The study evaluation schedule is summarized in Table 4-3.

Table 4-3  
Schedule of Evaluations

Evaluation	Assessments Before and After the Coronary Angioplasty Procedure/Study Drug Infusion												
	Baseline	Hours Post Procedure									Discharge	Post-infusion	
		EOP <sup>1</sup>	1	2	3	4	6	12	18	24		30 Days	6 Mos.
Medical/Medication History	X										X	X	
Physical Examination	X									X	X	X	
Vital Signs <sup>2</sup>	X		X	X	X	X	X	X	X				
12 Lead ECG	X										X	X	
Hematology <sup>3</sup>	X										X	X	
PT/aPTT	X	← PRN to maintain heparin levels →									X		
Serum Chemistry <sup>4</sup>	X										X		
Urinalysis <sup>5</sup>	X										X		
Angiographic Assessment <sup>6</sup>	X	X											X
Anti-Integrin Antibodies <sup>7</sup>	X											X	
Survey on Major Outcomes													X

- <sup>1</sup> EOP = immediately at the end of angioplasty procedure
- <sup>2</sup> Including heart rate, blood pressure, and temperature (temperature assessed less frequently than other vital signs). Vitals also assessed at infusion termination.
- <sup>3</sup> Including hemoglobin, hematocrit, total and differential leukocyte count
- <sup>4</sup> Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate
- <sup>5</sup> Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood
- <sup>6</sup> Follow-up tests performed in 900 patients at selected investigational sites
- <sup>7</sup> Testing performed only in the first 10 patients enrolled at each site
- <sup>8</sup> Testing performed in 30 patients enrolled at Duke University Medical Center

Table 4-3 (cont)  
Schedule of Evaluations

Evaluation	Assessments Before and After Study Drug Infusion													
	Baseline	Hours During Infusion						Infusion Term.		Hours Post-Infusion				Discharge & 30 Days
		1	6	8	12	18	24	Prior to	Term	4	8	12	16	
Vital Signs <sup>2</sup> (see also above)									X					
Platelet Count	X	X	X		X				X				X	
CK/CK-MB	X		X		X				X <sup>8</sup>				X	
Mass Balance (plasma) <sup>3</sup>				X		X	X			X	X	X		
Mass Balance (urine) <sup>3</sup>				X		X	X				X		X	
Pharmacokinetics								X						

- <sup>1</sup> EOP = immediately at the end of angioplasty procedure
- <sup>2</sup> Including heart rate, blood pressure, and temperature (temperature assessed less frequently than other vital signs). Vitals also assessed at infusion termination
- <sup>3</sup> Including hemoglobin, hematocrit, total and differential leukocyte count
- <sup>4</sup> Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate
- <sup>5</sup> Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood
- <sup>6</sup> Follow-up tests performed in 900 patients at selected investigational sites
- <sup>7</sup> Testing performed only in the first 10 patients enrolled at each site
- <sup>8</sup> Testing performed in 30 patients enrolled at Duke University Medical Center
- <sup>9</sup> CK/CK-MB was to be obtained at 24 hours or infusion termination

### STUDY ADMINISTRATION AND MONITORING

The study was randomized and monitored at the Duke University and Biometric Research Institute (BRI). The ECG Core Laboratory, located at the Duke University Medical Center, reviewed serial ECG tracings for changes consistent with MI. The Angiographic Core Laboratory, located at the Cleveland Clinic Foundation, reviewed angiograms for all enrolled patients and reviewed all follow-up angiograms. The Data and Safety Monitoring Committee (DSMC) was independent of the Sponsor, the Duke University, and the Cleveland Clinic. The DSMC included two cardiologists, a hematologist, a statistician, and an ethicist. Two Duke Coordinating Center statisticians served as non-voting committee members.

The Executive Committee consisted of Drs. Eric J. Topol (The Cleveland Clinic Foundation), Robert M. Califf (Duke University Medical Center), James E. Tcheng (Duke University Medical Center), and A. Michael Lincoff (The Cleveland Clinic Foundation) representing the investigators; Dr. Kerry L. Lee representing the Duke Coordinating Center; and Drs. Michael Kitt and Robert Swift representing COR Therapeutics. The Executive Committee also served as Steering Committee.

An independent Clinical Events Committee (CEC) that was blinded to patients' treatment assignments, reviewed all clinical data to determine efficacy and safety outcomes (death, MI, urgent or emergency coronary revascularization, stroke, and bleeding). Committee members included Duke University and Cleveland Clinic Foundation cardiologists. Cases were screened by CEC staff and referred to the CEC for evaluation of suspected clinical or safety events from the CRF or ECG "core" laboratory database. A Phase 1 review was performed by two independent CEC physicians. If their assessments agreed, the adjudication was considered final. Otherwise, the case was referred to Phase 2, which was a review by two independent CEC reviewers. Again, agreement resulted in resolution of the event status. Disagreement among Phase 2 reviewers resulted in referral to the Clinical Events Senior Committee. A 10% sampling of Phase 1 reviews that were in agreement was also sent to the Senior Committee to perform a quality assurance review.

The occurrence of a clinical event was also determined by the investigators. Both the CEC and the Investigator determination of the composite endpoint were compared between each Integrilin dosing regimen and placebo using pairwise comparisons. In addition, the effects of Integrilin on the incidence of abrupt closure during the index coronary angioplasty procedure were examined to determine whether Integrilin reduced ischemic complications of coronary revascularization

procedures by preventing abrupt closure.

Beside efficacy data, the CEC adjudicated the occurrence and severity of bleeding by the TIMI criteria, the etiology of all strokes, and the cause of all deaths. Safety was assessed based on the incidence of both bleeding and non-bleeding adverse events. Standard clinical laboratory tests and physical examination results were also compared among treatment groups.

Protocol Amendments: The study protocol was amended after the enrollment of the first patient as follows:

- change of sample size from 3000 to 3500 at 80 centers because of pairwise comparisons with adjustment of the  $\alpha$  level for multiple comparisons,
- shorter interval between start of study drug and interventional procedure,
- reduction of the initial heparin bolus from 150 to 100 units/kg,
- guidelines for intra coronary stents and endpoint stent placement,
- study drug discontinuation criteria and guidelines for early arterial sheath removal
- the time points at which the interim analyses were to be performed,
- statistical methodology for the primary endpoint analyses.

Amendment I added the following substudies: population PK, Integrilin antibody, angiographic follow-up. A second amendment added another substudy to evaluate the absorption and excretion (mass balance) of Integrilin at one participating center.

IMPACT II study results were presented at the European Society of Cardiology in Amsterdam on August 24, 1995. Two abstracts were presented at the American Heart Association (AHA) meeting in Anaheim, California, on November 15, 1995.

## STUDY DESIGN

Study size: The number of patients to be enrolled in the study was calculated on an assumed event rate of 11% in the absence of Integrilin. The assumption was based on the event rate of 12.8% from a study of high-risk PTCA and on the event rate of 13% for comparable PTCA patients from the Duke Databank for Cardiovascular Disease. Event rates from other trials, which included both high-risk and elective PTCA patients, ranged from 10% to 13%.

The study was designed to detect, with a power of 80%, a reduction of 33% in the incidence of primary composite endpoint from placebo to Integrilin (a decrease of the primary endpoint from 11.0% in placebo-treated patients to 7.4% in patients treated in either Integrilin group). The significance level for each pairwise comparison was specified as 0.035 to adjust for multiple comparisons.

The study population was increased from 3000 to 3500 right after the starting of the study with a protocol amendment. As a result of the second interim analysis, the DSMC recommended an increase in the sample size from 3500 to 4000 patients based on conditional power calculations using the observed rate in the control group and the hypothesized difference. No adjustment of the significance levels was made based on the results of the interim analyses.

Method of Treatment Assignment: Patients were enrolled in the study and simultaneously randomized according to a computer-generated schedule in blocks of nine in a 1:1:1 ratio. Patients were to be randomized 2 hours prior to PTCA, however, some patients were randomized before protocol eligibility was determined and never received study treatment. Randomization codes assigned to patients who did not receive treatment were not re-assigned.

Randomization was stratified by predicted clinical risk within each investigational site. The "High-risk" patients were defined as those experiencing either unstable angina or non-Q wave myocardial infarction (NQMI) or acute MI. Any patient not meeting the criteria for high risk was deemed "low risk" or "elective".

Patients were also classified as "high risk" based on CRF data. Analyses were performed using both enrollment and investigator (CRF) classifications of risk stratum. In addition, the EPIC criteria for high risk (acute evolving MI; UA, or angiographic criteria by the AHA and ACC) were used for a third analysis.

#### Protocol Definitions of UA, NQMI and MI:

UA or NQMI were defined by:

- a total creatine kinase (CK) less than two times the upper limit of normal at the time of enrollment and the presence of:
- angina at rest: including two or more episodes of angina at rest with ischemic ST segment or T wave abnormalities (i.e.,  $\geq 1$  mm ST segment depression [80 msec after the J point];  $\geq 1$  mm ST segment elevation [20 msec after the J point]; T Wave inversion or pseudonormalization);
- recurrent angina: recurrent angina with ischemic ST segment or T wave abnormalities as above while hospitalized and not prevented by standard pharmacological intervention; or
- early post-infarction angina: angina within 7 days of documented MI, with angina at rest accompanied by ischemic ST segment or T wave changes; or angina provoked by minimal exertion

Acute MI was defined by:

- ST segment elevation or reciprocal ST segment depression in at least two contiguous ECG leads in the presence of ischemic symptoms of at least 20 minutes duration, with the start of symptoms within 24 hours of the procedure.

This included patients who had angioplasty during acute MI without prior thrombolytics, or rescue angioplasty (within 24 hrs of thrombolytics for acute MI).

Study Drug Discontinuation and Withdrawal Criteria: Patients could be prematurely discontinued in case of clinical deterioration, requirement for emergency procedures, unusual or excessive bleeding, change in mental status or new neurological deficit, administration of open-label Dextran-40, other safety concerns ( i.e., thrombocytopenia or need for thrombolytic therapy).

### EFFICACY CRITERIA

Primary Outcome (Primary Endpoint): The primary endpoint was defined as the composite occurrence of death, MI, or urgent coronary revascularization (as determined by the CEC) within 30 days of randomization.

The components of the primary endpoint are defined in the protocol as follows:

- Death (all causes)
- Myocardial infarction (MI), including infarct extension and reinfarction.  
The definition of an endpoint MI was dependent upon whether or not the patient had sustained an acute MI within 24 hours of enrollment. In patients without a history of recent MI, or enrolled more than 24 hours following an acute MI, endpoint MI was defined as an elevation in the total CK-MB fraction to  $\geq 3$  times the ULN, or the development of new significant Q-waves  $\geq 0.04$  seconds duration in two or more contiguous leads. After hospital discharge, elevation of the total CK-MB fraction to  $\geq 2$  times the ULN or new significant Q-waves meeting the same criteria as noted above defined a new MI in the follow-up period. If the CK-MB fraction was not available, total CK values were analyzed, with endpoint infarction defined using the above quantitative criteria.  
For patients with an acute MI within 24 hours of the protocol intervention, reinfarction or extension was diagnosed based on one of two enzymatic criteria. In patients in whom serial assays of the CK-MB remained  $\geq 3$  times the ULN, a 25% decrease from a previous peak followed by a  $\geq 33\%$  increase in the CK-MB fraction was required. Otherwise, a 50% decrease from a previous peak followed by at least a 100% increase to  $\geq 3$  times the ULN was required. If CK-MB was not available, total CK was substituted.
- Urgent or emergency coronary revascularization, including stent implantation for threatened or manifest abrupt closure, repeat urgent or emergency angioplasty, or urgent or emergency coronary artery bypass graft surgery.

Secondary Outcome: Several secondary outcomes were evaluated, including:

- abrupt Closure (TIMI grade 0-1 flow in a vessel previously TIMI 2-3 flow.
- composite endpoint events at 6 months post- PTCA, (all procedures);
- effect of subgroup factors on the efficacy of Integrilin on the composite endpoint (demographic, risk strata, ACT during catheterization, stent, etc.)
- proportion of patients with urgent catheterization without angioplasty
- total time in the cardiac catheterization laboratory during angioplasty;
- proportion of patients with successful angioplasty (final stenosis  $< 50\%$  without a major clinical complication;
- proportion of patients receiving thrombolytic therapy during the angioplasty;
- cardiac cause-specific mortality, using the CEC-adjudicated cause of death.

Several substudies were also performed in addition to the PK profile (mass balance study) of Integrilin and the evaluation of the formation of anti-Integrilin antibodies. The substudies, to be analyzed and reported separately, included:

- Evaluation in 900 patients of the effect of Integrilin on minimal luminal diameter by angiography performed 6 months post-randomization;
- Nursing evaluation of maneuvers to control post-angioplasty bleeding.
- Comparison of economic, functional status, and quality of life outcomes in the three treatment groups through 6 months post-randomization.

### SAFETY EVALUATIONS

Safety was assessed in terms of bleeding and non-bleeding complications.

Bleeding Complications: Information on bleeding in the study report include:

- 1) the CEC adjudication of each patient according to the TIMI criteria,
- 2) the site and severity of bleeding events as assessed by the principal investigator,
- 3) the type and incidence of transfusion; and,
- 4) the laboratory indices of RBC loss.

Prior to determining the bleeding classification, the change in hemoglobin was adjusted for those patients who received red blood cell (RBC) transfusions and expressed in terms of bleeding index ( Hgb [or 1/3 Hct] + Units of RBC transfused).

The TIMI criteria and the Investigator's assessment of bleeding events were as described in IMPACT I and IMPACT High/Low studies.

Bleeding events were classified as serious if they were defined as serious or severe by the investigator, as major according to the CEC-adjudicated TIMI criteria, or if they required transfusion. Bleeding events leading to study drug discontinuation were not considered serious on that basis alone.

Non-Bleeding Adverse Events: Complications other than bleeding events noted by the Investigator were characterized as mild, moderate or severe, and as expected and unexpected.

Serious adverse events not reported as such on the CRF were identified based on criteria in the Protocol. Non-bleeding adverse events were classified as serious if the Investigator classified them as serious, or if they were a reason for discontinuation or unblinding of study drug, or were a stroke, myocardial ischemia, (MI was an efficacy endpoint), or a reason for extended hospitalization.

### ANALYSIS OF THE DATA

Each CRF was monitored and source document comparison of key safety and efficacy parameters was completed for all patients enrolled. The sponsor reviewed all monitoring reports and performed independent audits of 15 of the higher enrolling clinical sites. Biometric Research Institute, Inc., audited key efficacy and safety variables for missing, out-of-range, or inconsistent values and identified the discrepant records for resolution by the Duke Coordinating Center.

All statistical tests were performed at a significance level of 0.05 against a two-sided alternative hypothesis. The significance level for the composite efficacy variables (i.e., the CEC composite endpoint at 24 and 48 hours and at 30 days) for the comparison of each Integrilin dose group with the placebo group was predefined as 0.035 in the Protocol to approximate an adjustment for multiple comparisons. From an analysis performed after completion of the study, it was determined that this level of significance corresponds to an overall alpha of 0.067 when fully adjusted for multiple comparisons and interim analyses,

Efficacy analyses were performed on: 1) all patients randomized, and 2) the subset of patients who received any study medication and referred to as treated patients. Safety analyses include only treated patients.

Data originated from two sources: data collected on the CRF and data obtained from the CEC. CEC data were derived from an adjudication process which included information recorded by Investigators on the CRF and patient medical records. Endpoints adjudicated by the CEC were considered definitive and included the following outcomes: composite clinical primary endpoint (includes death, MI, or urgent coronary revascularization); bleeding classification; date and type of stroke, stent placement, coronary interventions, and CABG, cause of death. Any analyses of these outcomes based on the unadjudicated CRF data were considered secondary to the CEC-adjudicated outcomes.

Safety and efficacy data were reviewed by a DSMC during the study. There were three pre-specified meetings defined in the Protocol to evaluate safety after enrollment of 500 patients and to evaluate safety and efficacy after enrollment of 1/3 and 2/3 of patients.. The DSMC met five times during the course of the study and endpoint data were reviewed on three occasions. No safety concerns were noted, however, due to concerns about the number of patients available for analysis and the lower than expected event rate in the placebo group, additional meeting were held and it was recommended to enrollment to 4000 patients in order to maintain the 80% power to detect a 33% reduction in the composite endpoint.

Descriptive summaries were prepared for each treatment group for accountability, demographic, medical history, and treatment parameter data. Treatment groups were not compared with respect to these characteristics using statistical hypothesis tests, with the exception of those factors prespecified as subgroup variables for the analysis of outcomes. Homogeneity of the treatment groups was tested with respect to each of the following baseline variables: risk stratum at randomization; risk post-stratified based on CRF data; reason for revascularization; gender; weight group, age group, and history of hypertension, diabetes, and smoking.

**Efficacy Analyses:** The occurrence and timing of all CEC-adjudicated components of the composite endpoint were collected, with the initial one observed serving as the primary endpoint. A separate comparison between each Integrilin dose group and the placebo group was protocol defined. The CEC-adjudicated composite endpoint incidence through 30 days represents the primary analysis. Chi-square analysis at 24 and 48 hours was also performed.

Parallel analyses were performed for various components of the CEC-adjudicated composite endpoint: death; MI; death or MI; any urgent intervention; urgent CABG; and stent placement. Longer term maintenance of the benefit of Integrilin treatment was assessed by follow-up of these parameters through 6 months after randomization. The incidence of abrupt closure, specified in the Protocol as a secondary outcome measure, was assessed because of its relevance to the development of endpoint and to the mechanism of action of Integrilin.

The CEC composite endpoint at 24 hours and 30 days was also evaluated adjusting for Investigational Site by using Cochran-Mantel-Haenszel testing for each Integrilin dose compared to placebo. The Breslow-Day test was performed to assess the homogeneity across investigational sites of the results for the comparison of Integrilin treatment groups versus placebo. Sites with a total patient population of less than 30 and sites with enrollment of 30-59 patients were considered as single strata.

The incidence of the composite endpoint derived from the CRF data (referred to as the "Investigator's assessment" of the composite endpoint) and the various components (death, MI, urgent intervention) was compared using likelihood ratio  $X^2$  tests at 24 and 48 hours and 30 days.

The effect of various subgroup factors (gender; ethnicity; age; weight; risk stratum at randomization; risk post-stratified based on CRF data; EPIC risk; etc.) and of additional secondary efficacy measures (incidence of urgent diagnostic catheterization without angioplasty, the total time in the catheterization laboratory, the angioplasty success rate, the need for intra-procedural thrombolytics, and the incidence of and time to urgent intervention) were evaluated.

Safety Analyses:

Analysis of Adverse Events: Adverse events were classified for summarization as either non-bleeding or bleeding. Adverse events reported on the Complication CRF pages and the Serious Adverse Event Report form were coded using Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART). The CRF included spontaneously reported as well as elicited adverse events.

Summaries of the incidence of each of the following are provided for each treatment group: deaths; adverse events resulting in discontinuations (non-bleeding or bleeding); CEC-adjudicated bleeding complications; serious adverse events (non-bleeding or bleeding); and non-bleeding adverse events. Reasons for hospitalization were summarized separately from adverse events.

Laboratory Data Analysis: The change from baseline in each hematology, serum chemistry, and urinalysis parameter was summarized for each treatment group. Each integrilin dose was compared to placebo regarding the change from baseline to each specified time point using t-tests assuming equal variances. Confidence intervals for the mean differences between treatment groups were computed. Shift tables showing the change from baseline at each time point for each parameter with respect to normal ranges were created. "Marked" abnormalities were defined for laboratory parameters using the normal range at each site and the proportion of patients with each type of marked abnormality was calculated for each treatment group.

PATIENT POPULATION

A total of 4010 patients were randomized for the study and 3871 received study drug at 82 investigational sites. The randomization was balanced among treatment groups for both treated and untreated groups.

Twenty-four sites enrolled fewer than 25 patients, 31 sites enrolled 25-49 patients, 16 sites enrolled 50-99 patients, nine sites enrolled 100-149 patients, and two sites enrolled at least 150 patients. The largest site contributed 313 patients which represented 8% of the total patient population.

The difference in the reasons for revascularization approached statistical significance ( $p=0.053$ ) between the high dose Integrilin and placebo-treated groups, mainly because of the increased incidence of unstable angina in the high dose Integrilin-treated group.

Overall, 80.7% (3123/3871) of treated patients completed study drug treatment as per the Protocol (bolus plus a 20-24-hour infusion). A total of 748 (19.3%) did not receive treatment for the intended duration: 693 patients received less than 20

hours of infusion and 48 patients received more than 24 hours of study drug infusion. All patients treated with study medication received at least a study drug bolus, four patients received only the bolus dose.

Patients who were ready to be discharged prior to 24 hours post-procedure had their infusion stopped.

Notably, Integrilin-treated patients discontinued more frequently for adverse events, and placebo-treated patients discontinued more frequently for CABG, accidental IV problems, stent placement, and lesion condition or abortion of the procedure.

The reasons patients discontinued study drug treatment early (< 20 hours infusion) are summarized by treatment group in Table 5-3.

Table 5-3 Reason for study drug termination

Category	Integrilin High Dose	Integrilin Low Dose	Placebo
Patients who discontinued drug early (< 20 hours)	241 (18.7%)	214 (16.5%)	238 (18.5%)
Reason for early drug termination:			
Not due to Adverse Events:	87 (6.8%)	79 (6.1%)	105 (8.2%)
. Need for CABG	9 (0.7%)	14 (1.1%)	17 (1.3%)
. Need for Stent or Dextran	13 (1.0%)	12 (0.9%)	19 (1.5%)
. Clinical deterior.	0	1 (0.1%)	0
. Procedure aborted	27 (2.1%)	21 (1.6%)	32 (2.5%)
. Accidental	24 (1.9%)	17 (1.3%)	23 (1.8%)
. Thrombolytic Therapy	1 (0.1%)	2 (0.2%)	1 (0.1%)
. Other	13 (1.0%)	12 (0.9%)	13 (1.0%)
Due to Adverse Events	79 (6.1%)	58 (4.5%)	41 (3.2%)
Cause Unspecified	75 (5.8%)	77 (5.9%)	92 (7.2%)

The treatment assignments of 27 (0.7%) of the 3871 treated patients were unblinded during the study, mostly because of need for CABG, which occurred more frequently in the placebo group than in the low dose or high dose Integrilin-treated groups (6 vs 3 and 3 patients).

Five patients had less than 27 days follow-up, however, all treated patients were included in the 30-day follow-up which was defined as follow-up of at least 27 days post-randomization.

All patients who were entered in the study were candidates for 6-month follow-up.

A total of 144 patients were not included in the 6 months follow-up (table 5.5)

Table 5-5 Patients accountability for 6-month data

Total Enrollment	Integrilin High Dose N = 1286	Integrilin Low Dose N = 1300	Placebo N = 1285	Total N = 3871
Patients not included :	57	38	48	144
Reasons:				
Lost to F/U	25 (43.9%)	15 (39.5%)	25 (51.0%)	65 (45.1%)
Refused	11 (19.3%)	6 (15.5%)	9 (18.4%)	26 (18.1%)
Vital Status Only	21 (36.8%)	17(44.7%)	15 (30.6%)	53 (36.8%)

**Protocol Deviations:** Seven percent of the placebo patients and about 8% of the Integrilin patients were enrolled in the study despite pre-existing conditions that may have been protocol deviations (table 5-6). These patients were all included in the efficacy and safety analysis as the reasons for exclusion were based on patient safety concerns. In addition to deviations from exclusion criteria, certain procedural deviations also occurred, for example continuation of study drug longer than 24 hours or stent placement in the absence of abrupt closure. No attempt were made to identify such protocol deviations.

Table 5-6 Summary of Potential Protocol Deviations for Treated Patients by Treatment Group

Potential Protocol Deviation (by patient)	Integrilin High Dose N = 1286	Integrilin Low Dose N = 1300	Placebo N = 1285	Total N = 3871
Any Exclusion:	102 (7.9%)	110 (8.5%)	90 (7.0%)	302 (7.8%)
Severe Hypertension	39 (3.0%)	43 (3.3%)	26 (2.0%)	108 (2.8%)
History of Stroke	10 (0.8%)	7 (0.5%)	5 (0.4%)	22 (0.6%)
PT > 1.2 times control	44 (3.4%)	52 (4.0%)	54 (4.2%)	150 (3.9%)
Hematocrit <30%	8 (0.6%)	8 (0.6%)	5(0.4%)	21(0.5%)
Thrombocytopenia	0	2 (0.2%)	1(0.1%)	3 (0.1%)
Creatinine mg/mL	1 (0.1%)	0	0	1 (0.0%)
GI bleeding	0	1 (0.1%)	0	1 (0.0%)
Other study participat.	2 (0.2%)	4 (0.3%)	3 (0.2%)	9 (0.2%)

\* Patients could have more than one violation.

**Data Sets Analyzed:** Efficacy analyses were performed on the treated (primary analysis) and on the randomized populations. A total of 139 patients (3.5%) did not receive study medication mostly because of safety concerns, procedural difficulties prior to PTCA, alternative treatments or withdrawal of consent. The proportion of untreated patients was similar for each group. The decision not to treat was made by the investigator blinded to treatment assignment. The reasons

for omitting treatment are summarized in table 5-7

**Table 5-7**  
Investigator-Reported Reasons for Not Administering Study Drug

Reason Study Drug Not Administered	Integrelin High Dose (N=1333)	Integrelin Low Dose (N=1349)	Placebo (N=1328)
Randomized but No Study Drug Administered	47 (3.5%)	49 (3.6%)	43 (3.2%)
Reasons Not Treated with Study Drug			
Contraindication	5 (10.6%)	5 (10.2%)	5 (11.6%)
Lesion not PTCA suitable	16 (34.0%)	17 (34.7%)	15 (34.9%)
Hgb/Hct/platelets too low	0	0	1 (2.3%)
MD decision	13 (27.7%)	12 (24.5%)	15 (34.9%)
Inc/exc criteria not met	3 (6.4%)	2 (4.1%)	0
Consent withdrawn	1 (2.1%)	2 (4.1%)	2 (4.7%)
Other	9 (19.1%)	11 (22.4%)	5 (11.6%)

#### Baseline Characteristics

The proportion of patients was similar for demographic characteristics, cardiovascular history and risk factors, cerebrovascular history and non-vascular history, as well as for clinical presentation.

Overall, 75% of the treated patients were male, 92% were Caucasian, the mean age was 60 years and the mean weight was 85 kg.

Patients' predicted risks for ischemic events based on information reported at enrollment was similar to the CRF assessment (41% of patients based on enrollment information and 38% of patients based on CRF information were high risk). However, based on the EPIC risk stratum, 69% of patients were considered high risk, and in fact, the most commonly reported reason for revascularization was unstable angina which was reported for 66% (2570/3871) of treated patients. The difference in the reasons for revascularization between the high dose Integrelin and placebo-treated group was marginally significant ( $p=0.053$ ), mainly because of the increased incidence of unstable angina in the high dose Integrelin-treated group (high dose 68.8%, low dose 65.5%, placebo 64.9%).

The mean pre-treatment left ventricular ejection fraction (LVEF) was 56% overall, and was similar among treatment groups.

Cardiovascular History: Cardiovascular risk factors and cardiac clinical status at enrollment prior to angioplasty are summarized in tables 5-10 and 5-13

**Table 5-10**  
Cardiovascular History of Treated Patients\* by Treatment Group

Cardiovascular History	Integrelin High Dose (N=1286)	Integrelin Low Dose (N=1300)	Placebo (N=1285)	Total Treated (N=3871)
Previous Angina	959 (75.0%)	950 (73.4%)	931 (72.8%)	2840 (73.7%)
Previous MI	525 (41.0%)	528 (40.7%)	516 (40.2%)	1569 (40.6%)
Previous PTCA	399 (31.1%)	368 (28.3%)	372 (29.0%)	1139 (29.5%)
Previous CABG	217 (16.9%)	206 (15.8%)	190 (14.8%)	613 (15.8%)
Previous CHF	88 (6.9%)	76 (5.9%)	58 (4.5%)	222 (5.7%)

\* Patients with missing information for any parameter are not included in the denominator for that cell.

**Table 5-13**  
Summary of Clinical Presentation of Treated Patients\* by Treatment Group

Clinical Presentation	Integrelin High Dose (N=1286)	Integrelin Low Dose (N=1300)	Placebo (N=1285)	Total Treated (N=3871)
Risk Classification (questionnaire)				
High Risk	527 (41.0%)	532 (40.9%)	538 (41.9%)	1597 (41.3%)
Elective	759 (59.0%)	768 (59.1%)	747 (58.1%)	2274 (58.7%)
CRF Risk Classification				
High Risk	494 (38.4%)	493 (37.9%)	495 (38.5%)	1482 (38.3%)
Unstable Angina**	458 (35.6%)	449 (34.5%)	447 (34.8%)	1354 (35.0%)
Acute MI	36 (2.8%)	44 (3.4%)	48 (3.7%)	128 (3.3%)
Elective	782 (61.6%)	807 (62.1%)	790 (61.5%)	2389 (61.7%)
EPIC Risk Stratum (EPIC)				
EPIC Eligible (High Risk)	894 (69.5%)	903 (69.5%)	889 (69.2%)	2686 (69.4%)
Not EPIC Eligible	392 (30.5%)	397 (30.5%)	396 (30.8%)	1185 (30.6%)
Reason for Revascularization				
Asymptomatic	98 (7.6%)	123 (9.5%)	90 (7.0%)	311 (8.0%)
Pain only with MI	125 (9.7%)	132 (10.2%)	152 (11.8%)	409 (10.6%)
Stable angina	178 (13.8%)	183 (14.0%)	209 (16.3%)	580 (15.0%)
Unstable angina**	885 (68.8%)	851 (65.5%)	834 (64.9%)	2570 (66.4%)
Rest pain	440 (34.2%)	416 (32.0%)	432 (33.6%)	1288 (33.3%)
Post-infarct. Ischemia	144 (11.2%)	136 (10.5%)	131 (10.2%)	411 (10.6%)
Accelerating Pattern	509 (39.6%)	484 (37.3%)	473 (36.8%)	1466 (37.9%)
Pain w/ ECG changes	170 (13.2%)	157 (12.1%)	160 (12.5%)	487 (12.6%)
Missing	0	1	0	1
Pre-treatment LVEF***				
N	1046	1058	1039	3143
Mean (S.D.)	55.5 (12.64)	55.9 (12.68)	55.8 (12.20)	55.7 (12.51)
Median (Range)	58 (10,91)	59 (15,91)	60 (14,92)	59 (10,92)

\* Patients with missing information are not included in the denominator for that treatment group.

\*\* Difference in numbers under risk classification and reason for revascularization were due to the fact that documentation of revascularization was not limited to the time of enrollment, but to any time prior to randomization.

\*\*\* By any method

## TREATMENT PARAMETERS

Study Drug Administration: Study drug was administered generally as specified in the study protocol with less than 1% incorrect administration in any of the treatment groups. The mean and median duration of infusion was similar among treatment groups.

### Concomitant Medications:

Aspirin Use: A total of 80 patients (2.1%) did not receive aspirin: 2.1% in the high dose, 1.9% in the low dose, and 2.4% in the placebo group. Approximately 85% of treated patients received the protocol-specified aspirin dose (325 mg) prior to the procedure:

Heparin Dosing: Heparin was administered during the PTCA. Almost all patients received at least one bolus of heparin. The median number of boluses during the index catheterization was 2.0 for all groups. The mean total cumulative heparin dose received during the index catheterization was higher for placebo-treated patients (177.3 U/kg) than for high or low dose integrilin (169.1 and 169.6 U/kg respectively,  $p=0.0051$ ). Heparin administration information during 24 hours post-procedure was available for 2868 (74%) of the 3871 patients treated with study drug. There was no difference in heparin administration among groups during the 24 hours post procedure.

As expected because of the antiplatelet effect of Integrilin, the maximum ACTs recorded during the index catheterization were higher for Integrilin-treated patients than placebo-treated patients, even though placebo-treated patients received more heparin during the index catheterization. There was a statistically significant difference in the percentage of patients having maximum values above 350 seconds, with each Integrilin-treated group being higher than the placebo-treated group ( $p<0.001$ ).

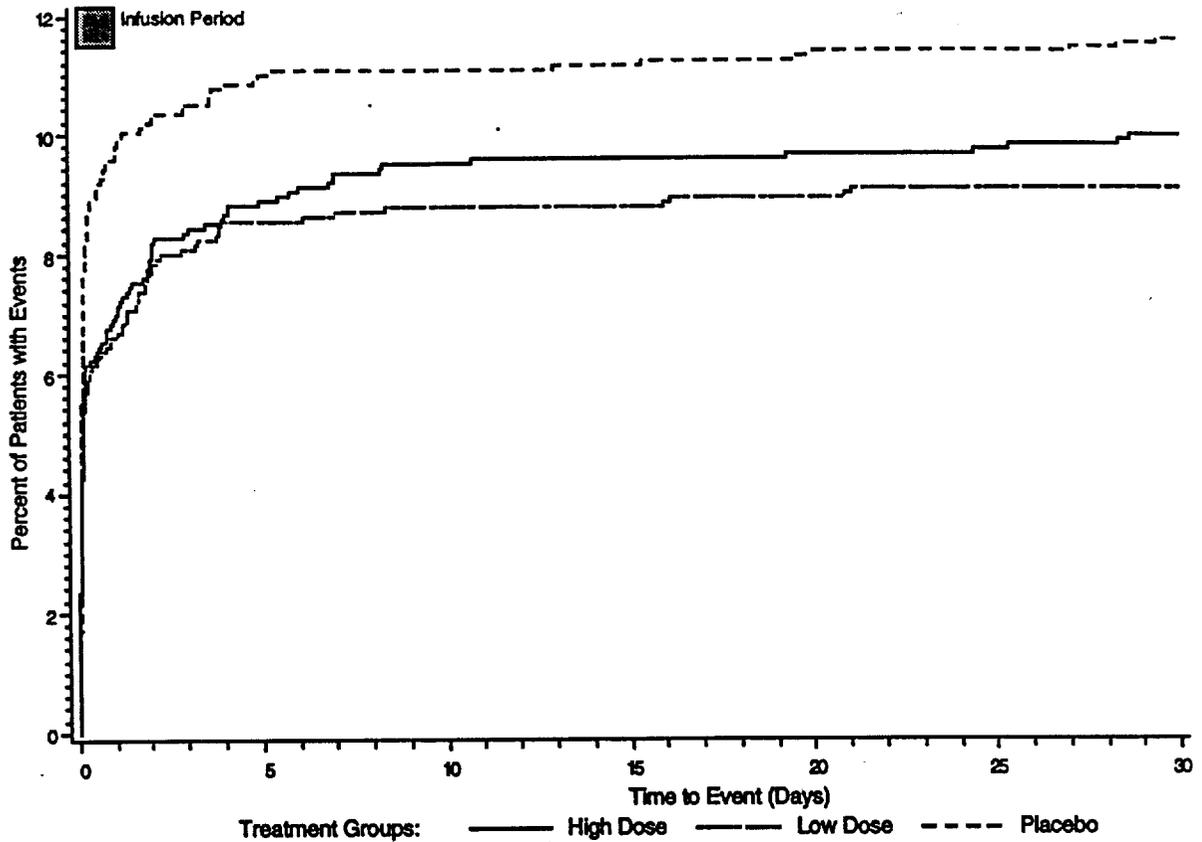
The peak aPTT values during the first 24 hours post-procedure were higher in the placebo-treated group than in the Integrilin-treated groups, but this difference was not statistically significant. This increase in aPTT values in the placebo-treated group is probably related to the fact that more heparin was administered to this group.

Thrombolytic Use: Thrombolytics were administered to fewer than 1% of patients within 24 hours prior to the catheterization procedure and the rate of use was similar among the treatment groups.

Other Concomitant Medications: These were similar among treatment groups.

The frequency of the composite endpoint over 30 days from treatment is shown in Figure 7-1

Figure 7-1: Kaplan-Meier Curve of the Frequency of the Composite Endpoint at 30 Days in Treated Patients



The 6-month data analysis differed from that done at 30 days because the revascularization procedures beyond 30 days were not necessarily related to thrombotic complications of angioplasty. Therefore, revascularizations performed between 30 days and 6 months were not adjudicated as to urgency by the CEC (death and MI continued to be adjudicated). Two different composite endpoints were used at 6 months: death and/or MI; and death, MI and/or any revascularization (urgent and elective).

The following table summarizes the relative reductions and analysis ('p') values during study drug administration (24 hours), at 48 hours, through the primary efficacy time point of 30 days. and at 6 month.

Incidence of CEC-Adjudicated Composite Events with Analysis ('p') Values in Treated Patients at 24 hours and at 30 days. Incidence of composite events at 6 months (not CEC-Adjudicated)

Time Point (composite end-points)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
24 hours (Death, MI, <u>Urgent</u> Intervention)	89 (6.9%)	86 (6.6%)	123 (9.6%)
% reduction*	28.1%	31.3%	--
P-value**	0.014	0.006	--
48 hours (Death, MI, <u>Urgent</u> Intervention)	102 (7.9%)	99 (7.6%)	131 (10.2%)
% reduction	22.5%	25.5%	--
P-value**	0.045	0.021	
30 Days (Death, MI, <u>Urgent</u> Intervention)	128 (10.0%)	118 (9.1%)	149 (11.6%)
% reduction*	13.8%	21.6%	--
P-value**	0.179	0.035	--
6 Month (Death, MI, <u>Any</u> Intervention)	379 (30.3%)	393 (30.9%)	403 (32.2%)
% reduction*	5.9%	4.0%	--
6 Month (Death and/or MI)	130 (10.3%)	136 (10.6%)	151 (11.9%)
% reduction*	13.9%	10.9%	

\* (Placebo rate minus Integrilin rate) divided by placebo rate

\*\* X<sup>2</sup> test of Integrilin vs. placebo

The Kaplan-Meier curves for the composite endpoints over 6 months are presented in Figures 7-2 and 7-3.

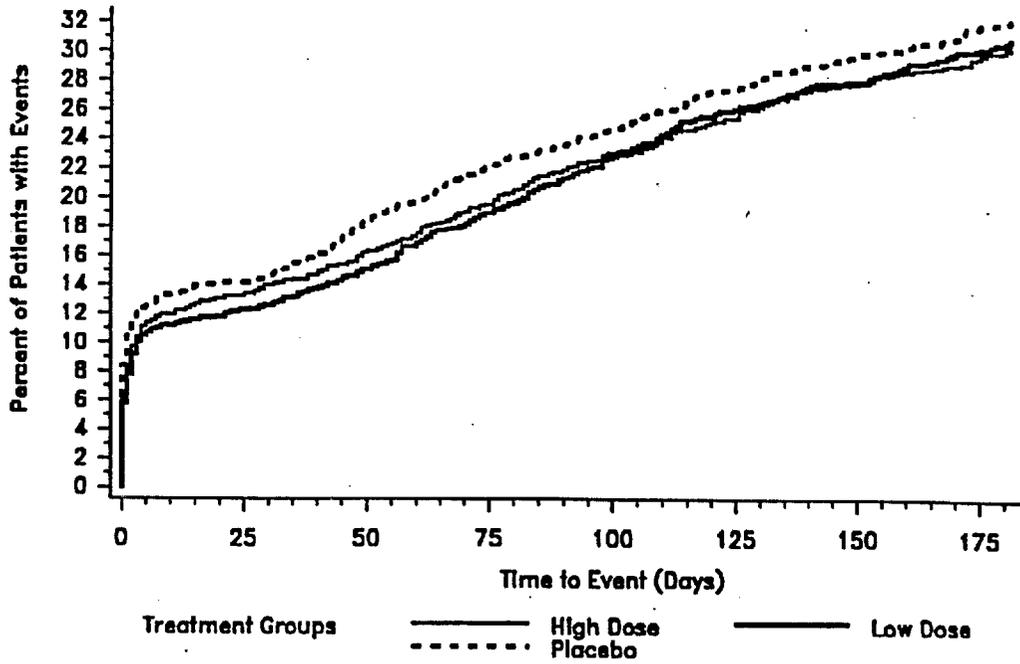


Figure 7-2: Frequency of Composite Endpoint (Death, MI, and/or Any Intervention) Over 6 Months for Treated Patients

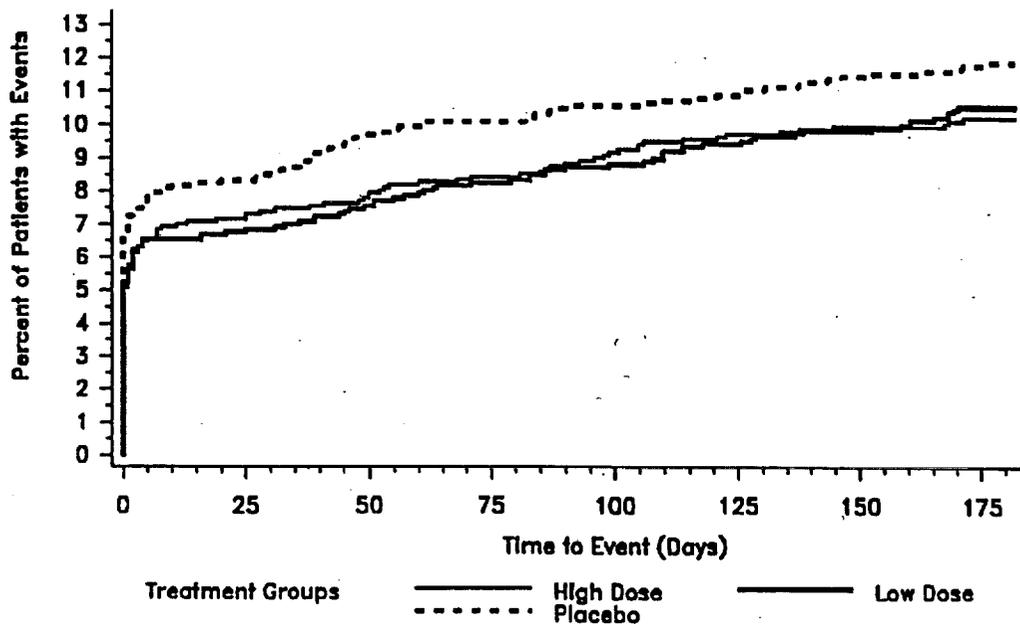


Figure 7-3: Frequency of Death and/or MI Over 6 Months for Treated Patients

2.0 Temporal presentation of composite endpoint

2.1 Abrupt Closure: To assess the effect of Integrilin in a temporal sequence, the incidence of abrupt closure (a secondary efficacy endpoint) was analyzed.

Both Integrilin regimens decreased the incidence of abrupt closure in association with the index angioplasty compared with placebo (table 7-3).

**Table 7-3** Incidence of Angiographically Observed Abrupt Closure During the Index Angioplasty Procedure by Treatment Group for Treated Patients

	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
Patients with Abrupt Closure	43 (3.3%)	36 (2.8%)	65 (5.1%)
% reduction*	33.8%	45.4%	--
P-value**	0.030	0.003	--

\* (Placebo rate minus Integrilin rate) divided by placebo rate. \*\*X<sup>2</sup> test of Integrilin vs. placebo

Abrupt closure was highly predictive of ischemic complications. Regardless of treatment, patients who experienced abrupt closure during the index angioplasty had a high incidence of clinical events (table 7-4).

The incidence of the composite endpoint was greater than 44% in all groups at all times among patients with abrupt closure, while it was less than 10% in all groups in which abrupt closure was not observed during the index angioplasty.

**Table 7-4** Incidence of Composite Endpoints by Abrupt Closure During the Index Angioplasty by Treatment Groups

Composite Endpoints	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
Patients with Abrupt Closure	N = 43	N = 36	N = 65
CEC adjudicated events at:			
24 hours	21 (48.8%)	16 (44.4%)	35 (53.8%)
48 hour	23 (53.5%)	17 (47.2%)	36 (55.4%)
30 days	24 (55.8%)	17 (47.2%)	38 (58.5%)
Patients without Abrupt Closure	N = 1243	N = 1264	N = 1220
CEC adjudicated events at:			
24 hours	68 (5.5%)	70 (5.5%)	88 (7.2%)
48 hours	79 (6.4%)	82 (6.5%)	95 (7.8%)
30 days	104 (8.4%)	101 (8.0%)	111 (9.1%)

Of the 139 patients randomized but not treated, 12 patients had a composite endpoint during the 30-day follow-up period: three patients were from the high dose Integrilin group, six were from the low dose Integrilin group, and two were from the placebo group.

**2.2 Incidence of Individual Components of the Composite Endpoint at 24 and 48 Hours and at 30 Days:** The data are summarized in the following table.

Incidence of each component of the CEC-Adjudicated Composite Events at 24 hours, 48 hours and 30 days

Post-Randomization Time Period	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
24 hours*			
Death	1 (0.1%)	0	1 (0.1%)
MI	66 (5.1%) +	71 (5.5%)	90 (7.0%)
Urgent CABG	13 (1.0%) +	13 (1.0%) +	28 (2.2%)
Urgent PTCA	13 (1.0%)	11 (0.8%) +	22 (1.7%)
Non-elective stent	7 (0.5%) +	7 (0.5%) +	17 (1.3%)
Total Composite	89 (6.9%) +	86 (6.6%) +	123 (9.6%)
48 hours*			
Death	5 (0.4%)	1 (0.1%)	4 (0.3%)
MI	75 (5.8%)	77 (5.9%)	95 (7.4%)
Urgent CABG	16 (1.2%)	15 (1.2%) +	30 (2.3%)
Urgent PTCA	20 (1.6%)	23 (1.8%)	24 (1.9%)
Non-elective stent	7 (0.5%) +	7 (0.5%) +	18 (1.4%)
Total Composite	102 (7.9%)	99 (7.6%) +	131 (10.2%)
30 days*			
Death	11 (0.9%)	6 (0.5%)	14 (1.1%)
MI	90 (7.0%)	86 (6.6%)	106 (8.2%)
Urgent CABG	26 (2.0%)	19 (1.5%) +	36 (2.8%)
Urgent PTCA	36 (2.8%)	35 (2.7%)	37 (2.9%)
Non-elective stent	7 (0.5%)	7 (0.5%)	18 (1.4%)
Total Composite	128 (10.0%)	118 (9.1%) +	149 (11.6%)

\* (A patient may have experienced more than one event in any given time period

+p-value <0.05 for X<sup>2</sup> test of Integrilin vs. placebo

At 24 and 48 hours, the incidence of MI was lower for Integrilin-treated patients compared to placebo-treated patients. At 24 hours, the difference between the high dose Integrilin group and the placebo group was statistically significant (p=0.046). There was a statistically significant decrease in the number of patients requiring urgent CABG in the Integrilin-treated patients compared to placebo at both 24 and 48 hours, while the incidence of urgent repeat angioplasty was significantly lower at 24 hours in the low dose Integrilin-treated group compared to the placebo group.

There was also a statistically significant decrease in patients requiring stent placement for abrupt closure in Integrilin-treated patients compared to placebo patients (p=0.024 in the high dose group; p=0.023 in the low dose group).

The incidence of the composite endpoint was similar for both Integrilin groups up to 5 days post-randomization, after which 14 additional events occurred in the high dose group, 7 in the low dose group, and 8 in the placebo group.

At 30 days, the reduction in both death and MI in the low dose Integrilin group persisted. The difference in total composite endpoint remained statistically significant ( $p=0.035$ ) for the low-dose Integrilin group compared to placebo. The reduction in urgent CABG in the low dose Integrilin-treated group was statistically significant compared to placebo ( $p=0.017$ ).

**2.3 Six Month Follow-up Analysis:** Revascularization procedures beyond 30 days are not necessarily related to thrombotic complications, therefore, these procedures performed between 30 days and 6 months were not adjudicated as urgent by the CEC. Thus the 6 month evaluation included either death and/or MI only or death, MI and any revascularization (Tables 7-9 and Fig 7-6)

Table 7-9 Incidence of CEC-Adjudicated Composite Endpoint of Death and/or MI at 24 hours, 30 Days and 6 months for Treated Patients.

Time Point (Events)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
24 hours (Death and/or MI)	67 (5.2%)	71 (5.5%)	90 (7.0%)
% reduction*	25.7	21.4	--
Absolute Reduction %	1.8	1.5	--
30 Days (Death and/or MI)	95 (7.4%)	89 (6.8%)	110 (8.6%)
% reduction*	14.0	20.9	--
Absolute Reduction %	1.2	1.8	--
6 Month (Death and/or MI)	130 (10.3%)	136 (10.6%)	151 (11.9%)
% reduction*	13.9	10.9	--
Absolute Reduction %	1.6	1.3	--

\* (Placebo rate minus Integrilin rate) divided by placebo rate

A numerical reduction in ischemic events with Integrilin therapy persisted at 6 months. The largest relative reduction in the components of the composite endpoint was in death and MI (table 7-11).

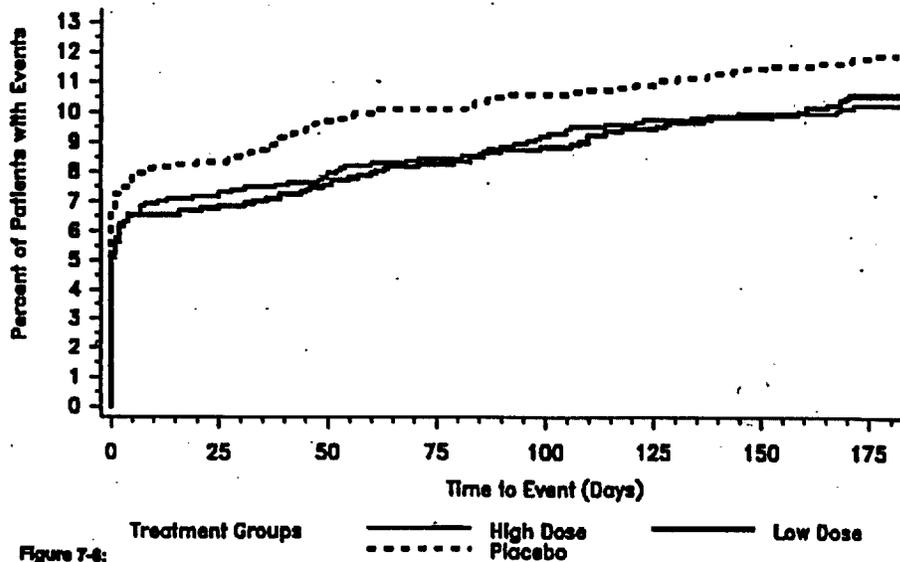
Table 7-11 Incidence of All Components of the CEC-Adjudicated Composite Endpoint\* for Treated Patients at 6 Months

Component Clinical Event	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
Death :			
Incidence	21	23	28
Event Rate*	1.7%	1.8%	2.2%
% Reduction**	22.7%	18.2%	--
MI			
Incidence	119	124	141
Event Rate*	9.4%	9.7%	11.1%
%Reduction**	15.3%	12.6%	--
CABG			
Incidence	112	124	122
Event Rate*	9.1%	9.9%	9.8%
% Reduction**	7.1%	-1.0%	--
Repeat Angioplasty			
Incidence	231	233	240
Event Rate*	18.7%	18.5%	19.5%
% Reduction**	4.1%	5.1%	--

\* Kaplan-Meier of Event Rate

\*\* (Placebo rate minus Integrilin rate) divided by placebo rate

Figure 7-6: Kaplan-Meier Curves of the Frequency of Composite Endpoint of Death and/or MI Over 6 Months for Treated Patients



### 3.0 Composite Efficacy Endpoints of Death, MI, and/or Any Interventions

Patients underwent non-urgent or elective interventions throughout the study period. Table 7-10 and Fig. 7.7 illustrate the frequency of the composite efficacy endpoints, including any coronary revascularization procedures up to 6 months. Elective interventions at 24 hours included stents placed at the time of the index angioplasty (33 Integrilin high-dose, 36 low dose, and 30 placebo patients).

Table 7-10 Incidence of CEC-Adjudicated Death, MI or Any Coronary Revascularization at 24 hours, 30 days and 6 months in Treated Patients

Time Point (composite end-points)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
24 hours (Death, MI, Any Intervention)	142 (11.0%)	141(10.8%)	176 (13.7%)
% reduction	19.7%	21.2%	--
Absolute Reduction	2.7%	2.9%	--
30 Days (Death, MI, Any Intervention)	213 (16.6%)	199 (15.3%)	223 (17.4%)
% reduction	4.6%	12.1%	--
Absolute Reduction	0.8%	2.1%	--
6 Month (Death, MI, Any Intervention*)	379 (30.3%)	393 (30.9%)	403 (32.2%)
% reduction	5.9%	4.0%	--
Absolute Reduction	1.9%	1.3%	--

\* Kaplan-Meier of Event Rate

Figure 7-7: Kaplan-Meier Curves of the Frequency of Composite Endpoint of Death, MI and/or Any Intervention Over 6 Months in Treated Patients

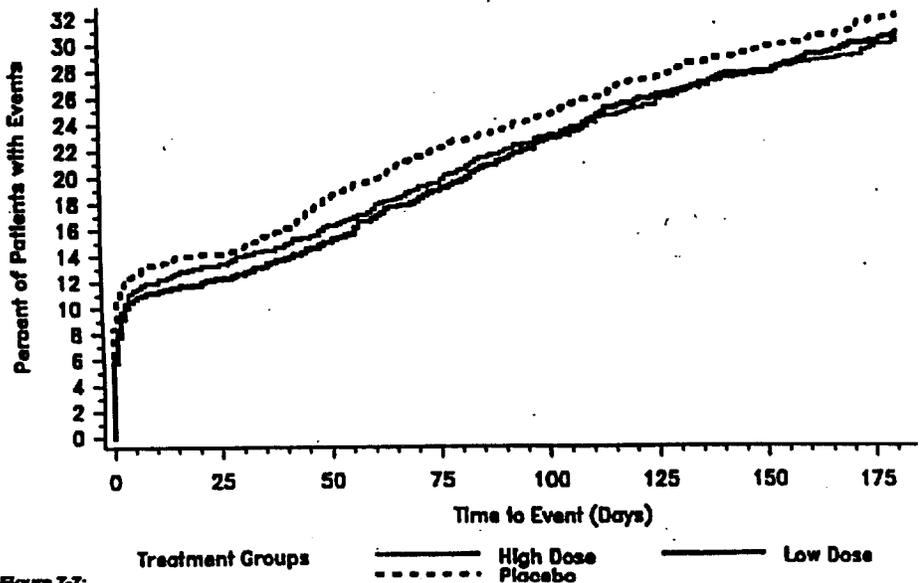


Figure 7-7:

#### 4.0 Dose Response and the Composite Endpoint

The Impact study was not designed to demonstrate an efficacy dose response. Two infusion doses were selected mainly to detect safety differences.

Most events (60-72% of the 30 day events) occurred during the period of effect of the common bolus dose of 135 ug/kg. Both infusion regimens resulted in similar incidence of clinical events until 5 days post-randomization, after which there was a small increment of events in the high dose group at 30 days followed by a slightly lower incidence of events in the high dose compared to the low dose group at 6 months. This difference is unlikely to represent a true dose-related effect.

#### 5.0 Randomized vs. Treated Patient Analyses

In addition to the efficacy analysis that includes all patients who received any portion of study agent (the 'treated patient' population), an analysis of all randomized patients was performed to determine consistency with the treated patient analysis and to exclude bias.

At 24 hours, the results were similar for the two population analyses, however, the therapeutic benefit was no longer statistically significant at the primary 30-day analysis time point. The results of the efficacy analyses for the two study populations are compared in Table 7-12.

**Table 7-12** Incidence of CEC-Adjudicated Composite Events at 24 Hours and 30 Days in Randomized and Treated Patients

Time Point	High Dose vs Placebo	Low Dose vs Placebo	High Dose vs Placebo	Low Dose vs Placebo
	Randomized Patients		Treated Patients	
24 Hours: Integrilin	7.0% (93/1333)	6.8% (92/1349)	6.9% (89/1286)	6.6% (86/1300)
	Placebo 9.3% (124/1328)	9.3% (124/1328)	9.6% (123/1285)	9.6% (123/1285)
%Reduction* (p-value)	24.7% (0.026)	26.9% (0.017)	28.1% (0.014)	31.3% (0.006)
30 Days: Integrilin	9.9 % (132/1333)	9.2% (124/1349)	10.0 % (128/1286)	9.1% (118/1300)
	Placebo 11.4% (151/1328)	11.4% (151/1328)	11.6% (149/1285)	11.6% (149/1285)
% Reduction* (p-value)	13.2% (0.219)	19.3% (0.063)	13.8% (0.179)	21.6 % (0.036)

\* (Placebo rate minus Integrilin rate) divided by placebo rate

\*\*X<sup>2</sup> tests of Integrilin vs. placebo

6.0 Composite Endpoint by Clinical Risk Strata

In order to balance the randomization, patients were prospectively stratified into a high-risk and an elective (low-risk) group at randomization. The patient's predicted risk of ischemic events was also assessed in the CRF by the investigator. The enrollment and the CRF risk assessments were similar. An additional risk assessment was made using the EPIC study criteria (clinical and angiographic). Of the three methods described (questionnaire at time of randomization, investigator assessment from CRF, EPIC study), the analysis by risk strata was done using the investigator-determined risk assessment.

Both Integrilin-treated groups had fewer events in the elective stratum than in the high-risk stratum at 30 days. However, the placebo-treated patients in the high-risk stratum did not have a higher incidence of events than placebo-treated patients in the elective stratum at either 24 hours or 30 days. Therefore, the prospectively defined criteria for identifying risk was not predictive of events (table 7-13 and Fig 7-10). It must be noted that, in fact, the method of risk assessment used did not agree with the entry diagnosis of UA (high risk) for 2/3 of patients.

**Table 7-13**  
Incidence of CEC-Adjudicated Composite Endpoint at 24 Hours and 30 Days for Treated Patients by Investigator Determined Risk Strata (CRF) and Treatment Group

CRF Risk Stratum	Integrilin High Dose (N=1288)	Integrilin Low Dose (N=1300)	Placebo (N=1288)
<b>24 Hours</b>			
<b>High Risk</b>			
Composite Endpoint	36 (7.3%)	36 (7.3%)	46 (9.3%)
Death	1 (0.2%)	0	1 (0.2%)
Myocardial Infarction	25 (5.3%)	29 (5.9%)	34 (6.9%)
Urgent/Emergency Revascularization	6 (1.2%)	7 (1.4%)	11 (2.2%)
Emergency/Urgent CABG	5 (1.0%)	6 (1.2%)	10 (2.0%)
Stent Placement	2 (0.4%)	2 (0.4%)	5 (1.0%)
<b>Elective</b>			
Composite Endpoint	53 (8.7%)	60 (8.2%)	77 (9.7%)
Death	40 (6.1%)	42 (5.2%)	36 (7.1%)
Myocardial Infarction	7 (0.9%)	4 (0.5%)	11 (1.4%)
Urgent/Emergency Revascularization	6 (1.0%)	7 (0.9%)	18 (2.3%)
Emergency/Urgent CABG	5 (0.8%)	5 (0.6%)	12 (1.5%)
Stent Placement			
<b>30 Days</b>			
<b>High Risk</b>			
Composite Endpoint	51 (10.3%)	57 (11.0%)	57 (11.5%)
Death	5 (1.0%)	5 (1.2%)	7 (1.4%)
Myocardial Infarction	36 (7.3%)	38 (7.7%)	40 (8.1%)
Urgent/Emergency Revascularization	13 (2.6%)	14 (2.8%)	17 (3.4%)
Emergency/Urgent CABG	11 (2.2%)	11 (2.2%)	13 (2.6%)
Stent Placement	2 (0.4%)	2 (0.4%)	6 (1.2%)
<b>Elective</b>			
Composite Endpoint	77 (8.7%)	61 (7.6%)	82 (11.0%)
Death	3 (0.4%)	0	7 (0.9%)
Myocardial Infarction	54 (6.8%)	48 (5.9%)	66 (8.4%)
Urgent/Emergency Revascularization	23 (2.8%)	11 (1.4%)	20 (2.6%)
Emergency/Urgent CABG	15 (1.8%)	8 (1.0%)	23 (2.9%)
Stent Placement	5 (0.6%)	5 (0.6%)	12 (1.5%)

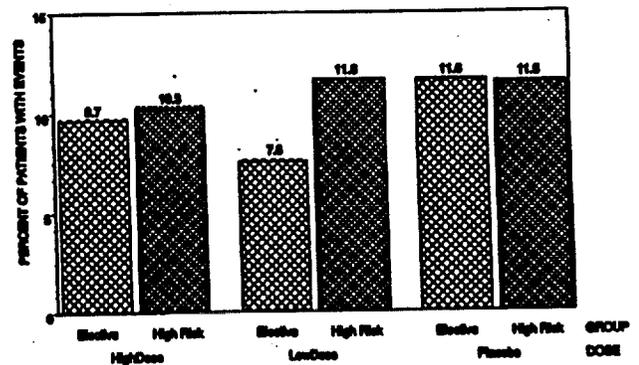


Figure 7-10: Incidence of CEC-Adjudicated Composite Endpoint at 30 Days Treated Patients by Investigator Determined Risk Stratification (CRF) and Treatment Group

[Source: Summary Tables E-62 and E-63; Summary Listing L-65]

### 7.0 Investigators' Assessment of the Composite Efficacy Endpoint

Investigators reported a lower incidence of clinical events - particularly MIs - than the CEC for both Integrilin regimens compared to placebo.

At 24 hours, the low dose Integrilin group experienced a 43% decrease ( $p=0.001$ ) and the high dose Integrilin group a 42% decrease ( $p=0.002$ ) in the incidence of the composite endpoint compared to placebo. At 48 hours, the reductions were 34% ( $p=0.011$ ) and 32% ( $p=0.022$ ) for the low and high dose groups, respectively. At 30 days, the low dose group maintained a statistically significant decrease of 28% ( $p=0.025$ ), while the decrease of 18% in the high dose group was not statistically significant when compared to placebo.

The incidence of the composite endpoint and of component events as assessed by the Investigators and by the CEC for each treatment group are shown in Table 7-14

**Table 7-14** Incidence of the Composite Endpoint and of Each Component Based on the Investigator's Assessment for Treated Patients by Treatment Group

Post-Randomization Time Period	Investigators' Assessment of Endpoints			CEC-Adjudicated Endpoints		
	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
<b>24 hours*</b>						
Death	1 (0.1)	0	1 (0.1)	1 (0.1)	0	1 (0.1)
MI	19 (1.5)	26 (2.0)	32 (2.5)	66 (5.1) +	71 (5.5)	90 (7.0)
Urgent CABG	15 (1.2)	11 (0.8) †	19 (1.5)	13 (1.0) +	13 (1.0) +	28 (2.2)
Urgent PTCA	16 (1.2)	15 (1.2)	31 (2.4)	13 (1.0)	11 (0.8) +	22 (1.7)
Non-elec. stent	3 (0.2) †	4 (0.3)	11 (0.9)	7 (0.5) +	7 (0.5) +	17 (1.3)
<b>Composite</b>	<b>46 (3.6) †</b>	<b>45 (3.5) †</b>	<b>79 (6.1)</b>	<b>89 (6.9) +</b>	<b>86 (6.6) +</b>	<b>123 (9.6)</b>
<b>48 hours*</b>						
Death	5 (0.4)	1 (0.1)	4 (0.3)	5 (0.4)	1 (0.1)	4 (0.3)
MI	22 (1.7)	30 (2.3)	33 (2.6)	75 (5.8)	77 (5.9)	95 (7.4)
Urgent CABG	21 (1.6)	18 (1.4) †	20 (1.6)	16 (1.2)	15(1.2) +	30 (2.3)
Urgent PTCA	17 (1.3)	16 (1.2)	31 (2.4)	20 (1.6)	23 (1.8)	24 (1.9)
Non-elec. stent	3 (0.2) †	4 (0.3)	11 (0.9)	7 (0.5) +	7(0.5) +	18 (1.4)
<b>Composite</b>	<b>56 (4.4) †</b>	<b>54 (4.2) †</b>	<b>82 (6.4)</b>	<b>102 (7.9)</b>	<b>99(7.6) +</b>	<b>131 (10.2)</b>
<b>30 Days*</b>						
Death	11 (0.9)	6 (0.5)	14 (1.1)	11 (0.9)	6 (0.5)	14 (1.1)
MI	27 (2.1)	35 (2.7)	38 (3.0)	90 (7.0)	86 (6.6)	106 (8.2)
Urgent CABG	32 (2.5)	28 (2.2)	28 (2.2)	26 (2.0)	19(1.5) +	36 (2.8)
Urgent PTCA	26 (2.0)	19 (1.5) †	36 (2.8)	36 (2.8)	35 (2.7)	37 (2.9)
Non-elec. stent	3 (0.2) †	4 (0.3)	11 (0.9)	7 (0.5)	7 (0.5)	18 (1.4)
<b>Composite</b>	<b>80 (6.2)</b>	<b>70 (5.4) †</b>	<b>97 (7.5)</b>	<b>128 (10.0)</b>	<b>118 (9.1)*</b>	<b>149 (11.6)</b>

\*A patient may have experienced more than one event in any given time period  
†p-value <0.05 for c 2 test of Integrilin vs. placebo

As noted in table 7-14, there were discrepancies between the two assessments over the 30-day monitoring period which are summarized in Table 7-15 and 7-16.

**Table 7-15 Consistency of Endpoints within 30 days - CEC vs. Investigators in treated patients**

	CEC	Investigator	Difference	CEC-Yes Investigator-No	Investigator-Yes CEC-No
Death	31	31	0	0	0
MI	282	100	182	200	18
Urgent CABG	81	81	0	4	4
Urgent PTCA	108	88	20	27	7
Endpoint Stent	32	18	14	15	1
Composite Endpoint	395	247	148	169	21

\* Kaplan-Meier of Event Rate

\*\* (Placebo rate minus Integrilin rate) divided by placebo rate

**Table 7-16 Distribution of Patients Reaching the Composite Endpoint According to the CEC and the Investigators by Treatment Group**

	High Dose Integrilin	Low Dose Integrilin	Placebo
CEC-Yes Investigator-Yes	71 (5.5%)	62 (4.8%)	93 (7.2%)
CEC-yes Investigator-No	57 (4.4%)	56 (4.3%)	56 (4.4%)
CEC-No Investigator-Yes	9 (0.7%)	8 (0.6%)	4 (0.3%)

There were 148 events in the total composite endpoint where the CEC and investigators had a difference in assessment of an event. There was a similar distribution of events among the three treatment groups of patients in whom the CEC decided that an event had occurred when the Investigators did not call an event as having occurred. There were only 21 events called by the Investigators where the CEC did not agree. These events were more frequent in the Integrilin groups (9 in the high dose group, 8 in the low dose group) compared to the placebo group (4 events).

The CEC assessment of events led to a higher incidence of the components of the composite endpoint compared to the on-site Investigator. The difference of 200 events was due primarily to the identification of relatively small post-angioplasty MIs by the CEC based on elevations of CK and/or CK-MB over time. Thus, the difference in the Investigators' assessment from the CEC assessment is primarily due to the identification of post-angioplasty MIs.

## 8.0 Components of the Composite Endpoint

### 8.1 Effect of treatment on the first and on the most severe endpoint:

The analysis of the components of the composite efficacy endpoint displayed as: 1) only the most severe component experienced by patients who reach the composite endpoint, 2) only the initially occurring events, indicate that Integrilin-treated patients experienced fewer severe events and a lower overall incidence of all component events. Patients may or may not have qualified for the composite endpoint in the same time period they experienced the most severe event.

The most severe and the first event for each patient reaching the composite endpoint are summarized in the following table.

Incidence of the Most Severe or First Event of the Composite Endpoint by Treatment Group

Post-Randomization Time Period	Most Severe Event and Composite Endpoints			First Event and Composite Endpoints		
	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
<b>24 hours*</b>						
Death	1 (0.1)	0	1 (0.1)	0 (0.0)	0	0 (0.0)
MI	66 (5.1)	71 (5.5)	89 (6.9)	63 (4.9)	69 (5.3)	86 (6.7)
Urgent CABG	8 (0.6)	6 (0.5)	17 (1.3)	9 (0.7)	5 (0.4)	17 (1.3)
Urgent PTCA	9 (0.7)	4 (0.3)	7 (0.5)	11 (0.9)	7 (0.5)	11 (0.9)
Non-elec.stent	5 (0.4)	5 (0.4)	9 (0.7)	6 (0.5)	5 (0.4)	9 (0.7)
<b>Composite</b>	<b>89 (6.9)</b>	<b>86 (6.6)</b>	<b>123 (9.6)</b>	<b>89 (6.9)</b>	<b>86 (6.6)</b>	<b>123 (9.6)</b>
<b>48 hours*</b>						
Death	5 (0.4)	1 (0.1)	4 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)
MI	73 (5.7)	77 (5.9)	91 (7.1)	70 (5.4)	74 (5.7)	91 (7.1)
Urgent CABG	10 (0.8)	7 (0.5)	18 (1.4)	10 (0.8)	6(0.5)	18 (1.4)
Urgent PTCA	10 (0.8)	9 (0.7)	8 (0.6)	15 (1.2)	13 (1.0)	12 (0.9)
Non-elec. stent	4 (0.3)	5 (0.4)	10 (0.8)	6 (0.5)	5(0.4)	10 (0.8)
<b>Composite</b>	<b>102 (7.9)</b>	<b>99 (7.6)</b>	<b>131 (10.2)</b>	<b>102 (7.9)</b>	<b>99(7.6)</b>	<b>131 (10.2)</b>
<b>30 Days*</b>						
Death	11 (0.9)	6 (0.5)	14 (1.1)	3 (0.2)	3 (0.2)	3 (0.2)
MI	84 (6.5)	83 (6.4)	96 (3.0)	81 (6.3)	80 (6.2)	99 (7.7)
Urgent CABG	15 (1.2)	10 (0.8)	18 (2.2)	13 (1.0)	8 (0.6)	19 (1.5)
Urgent PTCA	14 (1.1)	14 (1.1)	13 (2.8)	25 (1.9)	22 (1.7)	18 (1.4)
Non-elec. stent	3 (0.2) †	5 (0.4)	8 (0.9)	6 (0.5)	5 (0.4)	10 (0.8)
<b>Composite</b>	<b>128 (10.0)</b>	<b>118 (9.1)</b>	<b>149 (11.6)</b>	<b>128 (10.0)</b>	<b>118 (9.1)*</b>	<b>149 (11.6)</b>

\*A patient may have experienced more than one event in any given time period

At 24 and 48 hours and at 30 days post-randomization, MI was the most commonly experienced first event for patients in all treatment groups. At 30 days, there were more deaths in the placebo group (14) than in either of the Integrilin treatment groups (six in the low dose group, 11 in the high dose group).

The greatest difference between placebo-treated and Integrilin-treated patients was in the incidence of CEC-adjudicated MI, which at 24 hours occurred in 6.9% of placebo patients, 5.5% of low dose Integrilin patients, and 5.1% of high dose Integrilin patients. Differences among the treatment groups were still present but less prominent at 30 days post-randomization. Urgent revascularizations and stent placement occurring as the most severe event were less common overall. The smallest differences among the treatment groups were noted among patients experiencing urgent intervention as the most severe component.

### 8.2 Effect of treatment on the incidence of subtypes of MI:

In the IMPACT II study, the greatest effect of Integrilin was on MI. The CEC determined the MI subtypes for informational purposes as part of the adjudication process. The subtypes of MIs are defined as follows:

Q wave = New Q wave on ECG

Large enzyme = Peak CK > 5 x upper limit of normal

At 30 days, the incidence of Q-wave and Large Enzyme MIs was numerically lower in the Integrilin-treated groups. The data are summarized in table 7-19

**Table 7-19**  
Incidence of Subtypes of MIs and the Corresponding CEC-Adjudicated Composite of Death and/or MI for Treated Patients by Treatment Group

	Integrilin High Dose	Integrilin Low Dose	Placebo
<b>At 24 Hours</b>			
Any MI p* value vs. placebo	66 (5.1%) 0.046	71 (5.5%) 0.104	90 (7.0%)
Q-Wave MI p* value vs. placebo	4 (0.3%) 0.361	7 (0.5%) 0.963	7 (0.5%)
Large Enzyme MI p* value vs. placebo	35 (2.7%) 0.031	39 (3.0%) 0.081	55 (4.3%)
Composite Endpoint With Death, Q-Wave And/or Large Enzyme MI and Urgent Intervention p* value vs. placebo	65 (5.1%) 0.021	64 (4.9%) 0.014	93 (7.2%)
<b>At 30 Days</b>			
Any MI p* value vs. placebo	90 (7.0%) 0.232	86 (6.6%) 0.113	106 (8.2%)
Q-Wave MI p* value vs. placebo	13 (0.1%) 0.481	12 (0.9%) 0.333	17 (1.3%)
Large Enzyme MI p* value vs. placebo	53 (4.1%) 0.164	52 (4.0%) 0.118	66 (5.3%)
Composite Endpoint With Death, Q-Wave And/or Large Enzyme MI and Urgent Intervention p* value vs. placebo	105 (8.2%) 0.235	97 (7.5%) 0.083	122 (9.5%)

[Source: Summary Table E-1, E-2, E-4, E-13, E-14 and E-16; Summary Listing L-30]

\* p value from  $\chi^2$  Integrilin vs. placebo

## 9.0 Effect of Investigational Site on the Composite Endpoint

Two analyses were performed to investigate the effect of investigational site on the composite efficacy endpoint.

In the first analysis, sites with enrollments of <30 patients and sites with enrollments of 30 to 59 patients were pooled. Sites with higher enrollment were considered individually.

A Breslow Day test for homogeneity was performed that showed no evidence of inhomogeneity at 24 hours ( $p=0.24$  for the high dose and  $p=0.17$  for the low dose Integrilin groups compared to placebo) or at 30 days ( $p=0.07$  for the high dose and  $p=0.17$  for the low dose compared to placebo).

## 10.0 Subgroup, Covariate, and Multivariate Analyses:

Several analyses were undertaken to determine any factors that may have affected the response to Integrilin therapy.

- 1) A subgroup (or Covariate) analysis was undertaken to determine the effect of any of several subgroups on clinical response.
- 2) Subgroups were examined to determine whether the events that occurred in the high dose Integrilin-treated group between 24 hours and 30 days were associated strongly with any particular subgroup.

A Multivariate model was constructed to identify significant covariates and to adjust the analysis ('p') values for any baseline or other imbalances between treatment groups in order to investigate the robustness of the principal (unadjusted) analysis.

**10.1 Subgroup Analyses:** The efficacy of Integrilin as defined by the CEC composite endpoint was explored in several subgroups as defined by disease-specific factors, common diagnoses at baseline and standard demographics. Although the IMPACT II study was not powered to determine the definitive effects in subgroups, the following trends were observed (NDA Vol. 1.109, p.129, 131, 133, 135, 137):

- The distribution of events across different ages was not constant and no age-related effect of treatment with Integrilin was observed .
- Patients >74 kg had the greatest treatment effect associated with Integrilin.
- Men had greater treatment effect associated with Integrilin therapy than women. However, there was no gender difference if weight was taken into account.
- Race-related treatment effects could not be determined due to the small

number of non-Caucasian patients.

- Patients who underwent PTCA with a history of UA experienced a higher incidence of clinical events. Patients with UA had a lower incidence of events with both Integrilin regimens, whereas those without this history responded better to the high dose regimen. Patients with UA are more frequent in this category than in the category of patients with UA at the time of enrollment on which the stratification at randomization was based.
- Patients treated with Integrilin without a history of hypertension experienced a lower incidence of events than those with a history of hypertension.
- Patients with diabetes experienced a lower incidence of events than those without in all three treatment groups.
- A history of smoking had no effect on the response to Integrilin.
- Integrilin-treated patients receiving stents experienced a lower incidence of events than placebo patients receiving dextran, if Integrilin was continued during the procedure.
- Patients who did not receive aspirin in the placebo group had a higher incidence of events than patients in the placebo group who received aspirin. In addition, there was more than a 50% reduction in events in patients who did not receive aspirin but did receive Integrilin, although the number of patients in this subgroup is small.
- Patients with a duration of disease > 5 years and treated with Integrilin had a lower incidence of the composite endpoint compared to placebo patients. This effect was less consistent in patients with a disease duration of more than 5 years.
- Baseline platelet count was not associated with a trend in incidence of the composite efficacy endpoint.
- Maximum ACT > 350 seconds during the index procedure was correlated with an increased incidence of events. Integrilin tended to have a better effect in patients with an ACT within the target therapeutic range of 300-350 seconds compared to those patients treated with Integrilin that were either above or below the ACT target range.
- The greatest therapeutic benefit of treatment with Integrilin occurred in patients with a shorter duration of heparin infusion. This observation may be confounded, however, by the fact that many clinical events occurred early (within 5-6 hours) and often resulted in premature discontinuation of heparin infusion (e.g. emergency PTCA or CABG).
- No consistent effect of heparin infusion duration was observed on the incidence of the composite endpoint within treatment groups.
- Hyperlipidemia, history of previous CABG and family history of CAD were not correlated with the incidence of the primary endpoint.
- Patients with a previous history of PTCA had a similar incidence of events in all three treatment groups.

The subgroup analyses that were performed to demonstrate whether the events that occurred in the high dose Integrilin-treated group between 24 hours and 30 days were associated strongly with any particular subgroup indicate that these clinical events were seen over a wide range of subgroups.

**10.2 Multivariate Analysis:** This was performed to identify significant factors associated with an increased incidence of clinical events and to calculate their effect on the overall analysis. The purpose of this analysis was to determine whether the significance level of the unadjusted analysis was affected by any imbalances or unsuspected interactions of Integrilin with clinically significant factors.

Essentially, no imbalance in baseline or disease-specific factors that affected the results was demonstrated by the Multivariate analysis. The significance p-values for each dose group were consistent with the unadjusted analysis ( $p=0.027$  to  $0.059$  for the low-dose group and approximately  $0.2$  for the high-dose group).

A Multivariate time to event analysis using a Cox Proportional Hazards model was performed. The model was built considering risk assessment as reported on the CRF and using the following covariates: weight, age, gender, ethnicity, type of angioplasty procedure, culprit artery, use of a stent, maximum ACT, and history of diabetes, hypertension, hyperlipidemia, current smoking, and aspirin use.

Three covariates were identified as significant in both Integrilin dose groups: stent placement, maximum ACT and use of a Rotablator device during the index angioplasty:

- 1) Patients with initial procedure including stents had 3-5 fold greater event rates through 30 days than non-stent patients.
- 2) Patients with maximum ACT <350 had consistently lower rate through 30 days than otherwise.
- 3) Patients using rotational ablation angioplasty experienced 25-100% greater event rates through 30 days than otherwise.

All three relationships existed across treatment groups.

#### **ADDITIONAL SECONDARY ENDPOINTS**

The secondary endpoints that were analyzed (in addition to abrupt closure rates and event rates at 6 months) included:

- **Incidence of All Interventions:** This was assessed to determine whether the decrease in urgent interventions in patients receiving Integrilin was balanced by an increase in the incidence of non-urgent interventions. Integrilin-treated patients in both high and low dose treatment groups had a lower incidence of all coronary interventions compared to the placebo group. This effect was statistically significant in both groups at 24 hours, but not at 30 days.
  - **Time to Urgent Intervention Within 30 Days of Treatment Initiation:** In general, fewer Integrilin-treated patients had an urgent intervention and the time to the first urgent intervention was longer than for placebo-treated patients.
  - **Urgent Diagnostic Catheterization (Angiography) without Subsequent Angioplasty:** The need was lower in the Integrilin groups, the difference was not significant.
  - **Angioplasty Success (Clinical and Procedural):**  
The clinical angioplasty success rate was slightly higher among Integrilin-treated patients than among placebo-treated patients. The difference in success rates between the high dose Integrilin group (85.0%) and the placebo group (83.0%) was not statistically significant, but the difference between the incidence in the low dose Integrilin group (86.7%) and the placebo group was statistically significant ( $p = 0.008$ ).
- Procedural angioplasty success was defined as a post-procedural luminal stenosis of 50% or less in index lesions without an abrupt closure. The procedural angioplasty success rate was higher among Integrilin-treated patients than among placebo-treated patients. The difference in success rates between the high dose Integrilin-treated group (87.3%) and the placebo group (85.9%) was not statistically significant, but the difference between the incidence in the low dose Integrilin-treated group (88.6%) compared to the placebo-treated group was significant ( $p = 0.039$ ).
- **Cardiac Mortality:** The cause of death was adjudicated by the CEC and the cardiac (cause-specific) mortality rate examined as a secondary endpoint. The incidence of death due to cardiac causes within 30 days post-randomization was statistically significantly lower ( $p = 0.023$ ) in the low dose Integrilin-treated group (0.1%) than in the placebo-treated group (0.5%). The cardiac mortality rate in the high dose Integrilin group (0.5%) was identical to the placebo group.
  - **Intra procedural Thrombolytic Requirements:** Thrombolytics were administered during the index catheterization to 1.9% of placebo patients and to 1.2% of Integrilin-treated patients. The difference was not statistically significant.

## SAFETY EVALUATIONS

The safety evaluation in IMPACT II was performed only on patients who received study treatment (n = 3871).

The majority of adverse clinical events experienced by patients undergoing coronary angioplasty involve bleeding, events associated with the procedure itself, or symptoms of underlying disease.

### BLEEDING ADVERSE EVENTS

Bleeding events and their sequelae were recorded and analyzed by 3 methods:

1. The TIMI criteria as adjudicated by the CEC.
2. Frequency and severity of investigator-reported bleeding events
3. Incidence of transfusion of red blood cells, platelets, or plasma

Both bleeding and non-bleeding adverse events were assessed for two time periods: 1) from randomization to 24 hours after termination of study drug infusion; and, 2) from randomization to 30 days after initiation of study drug. Bleeding according to the TIMI criteria was determined over the 30-day study period.

Incidence of CEC-Adjudicated Bleeding Complications (TIMI Criteria): The incidence of minor bleeding was increased in patients receiving Integrilin, particularly in the high dose group. The incidence of major and minor bleeding as adjudicated by the CEC is presented in Table 8-2 and in Fig.8-1.

**Table 8-2 Incidence of CEC-Adjudicated Bleeding Complications (Major and Minor) in Treated Patients**

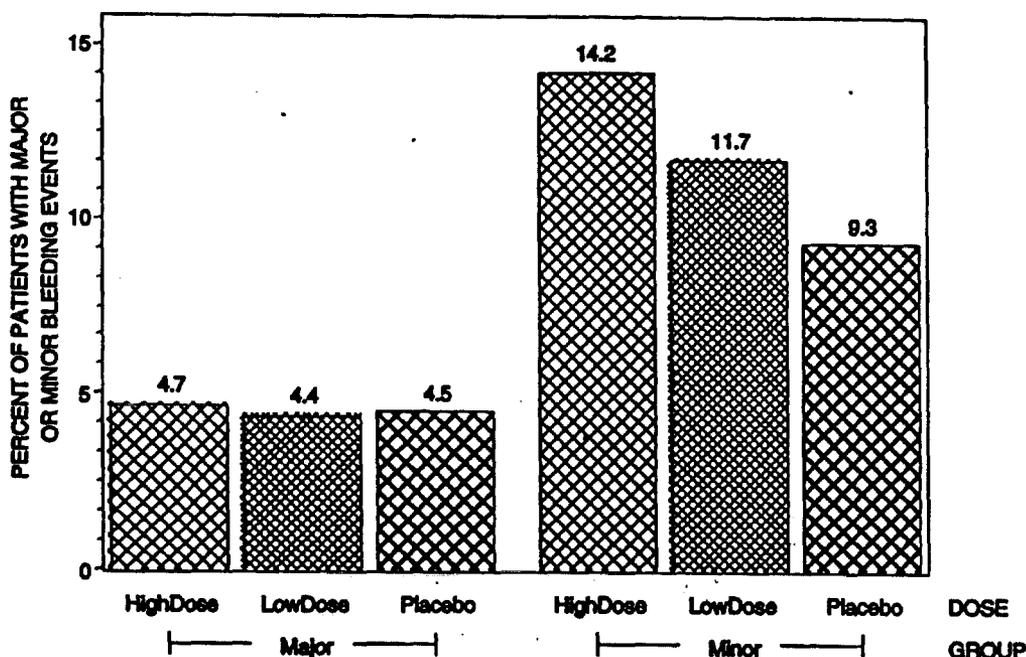
TIMI Bleeding	High Dose Integrilin	Low Dose Integrilin	Placebo
Total Patients*	1245	1249	1230
Major Bleeding	58 ( 4.7%)	55 ( 4.4%)	55 ( 4.5%)
Minor Bleeding	177 (14.2%)	146 (11.7%)	115 ( 9.3%)
Insignificant Bleeding	620 (49.8%)	650 (52.0%)	567 (46.1%)
No Bleeding	390 (31.3%)	398 (31.9%)	493 (40.1%)
Unresolved	41	51	55
Total Bleeding Events	1286	1300	1285

\* Patients with Bleeding Complications Adjudicated by the CEC. Patients with unresolved bleeding are not included in the denominator for that treatment group

Chi-square ( $\chi^2$ ) testing was performed for major and minor bleeding, comparing each Integrilin group to placebo. The tests were not statistically significant for major bleeding, but were significant for minor bleeding in the high dose Integrilin-treated group ( $p < 0.001$ ) and marginally significant ( $p = 0.057$ ) in the low dose Integrilin-treated group compared to placebo.

Of the 147 patients with unresolved CEC bleeding complications, slightly more than half had bleeding reported by the Investigator. None of these patients had a serious bleeding event or required any blood transfusions.

**Figure 8-1: Incidence of CEC-Adjudicated Major and Minor Bleeding Over 30 Days After Treatment Initiation for Treated Patients by Treatment Group**



**Bleeding Locations for Patients with Major and Minor Bleeding Events (TIMI Criteria)**

The femoral artery access site was the most common site of major and minor bleeding in patients receiving Integrilin or placebo. Intracranial bleeding occurred in 2/1286 (0.2%) patients in the high dose group, in 1/1300 (0.1%) patients in the low dose group and in 1/1285 (0.1%) placebo patients. The incidence of major GU, GI, and retroperitoneal bleeding was similar among treatment groups. CABG was commonly associated with major bleeding in all groups. Minor bleeding from the GU tract was more commonly noted in Integrilin-treated patients.

**Investigator-Reported Bleeding Events:** Investigator-reported bleeding events occurring up to 24 hr after infusion, are summarized, by severity, in Table 8-5.

**Table 8-5 Incidence of Investigator-Reported Bleeding Observed During Infusion or Within 24 Hours After Infusion Termination Stratified by Maximum Severity in Treated Patients by Treatment Group**

Maximum Severity of Bleeding Events	High Dose Integrilin (N = 1286)	Low Dose Integrilin (N = 1300)	Placebo (N = 1285)
Severe	13 ( 1.0%)	17 ( 1.3%)	11 ( 0.9%)
Moderate	136 (10.6%)	101 ( 7.8%)	73 ( 5.7%)
Mild	671 (52.2%)	699 (53.8%)	601 (46.8%)
Any	820 (53.8%)	817 (62.9%)	685 (53.3%)

\* Patients with Bleeding Complications Adjudicated by the CEC. Patients with unresolved bleeding are not included in the denominator for that treatment group

Severe bleeding was uncommon and similar in frequency among treatment groups. Treatment with Integrilin did result in more events classified as moderate and mild compared to placebo-treated patients.

The femoral artery access site accounted for the majority of reported bleeding sites, and was more commonly reported in the Integrilin-treated groups. In addition to bleeding at the access site, spontaneous gross hematuria, spontaneous hematemesis, oral bleeding, and epistaxis tended to be reported more often in the Integrilin- than placebo-treated groups, although the between group differences were small.

The incidence of bleeding events after the acute period of study drug administration showed a small increase in the percentage of patients who reported bleeding events. The femoral artery access site accounted for the majority of reported bleeding sites and was reported more frequently among Integrilin-treated patients.

**Transfusions:** The proportions of patients receiving from one to ten units of PRBCs, plasma and platelets were similar among treatment groups. Treatment with Integrilin did not increase the need for any blood product.

**Bleeding Excluding Patients Undergoing Coronary Artery Bypass Graft (CABG)**

**Surgery:** The incidence of major bleeding was lower in the subgroup of non-surgical (non-CABG) patients compared to the overall population in this study. However, the incidence of major bleeding was higher in both Integrilin groups (2.7%) than in the placebo group (1.7%) in this population, although the number of patients was small.

The incidence of minor bleeding was only slightly less than the total population. The most common site of bleeding (major and minor) was the femoral access site.

The requirement for transfusions in patients who did not undergo CABG was low.

The total number of patients requiring transfusions was greater in Integrilin-treated patients than in placebo-treated patients (high dose 4.0%, low dose 3.5%, and placebo 2.0%). The number of patients requiring platelet transfusions was very small (high dose 0.1%, low dose 0.2%, placebo 0.1%).

Bleeding in Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery: Integrilin therapy was associated with a lower incidence of major and minor bleeding events in patients who underwent CABG surgery.

Subgroup Analysis of Bleeding Risk: The risk of bleeding was assessed in several subgroups of patients defined by age, gender, ethnicity, weight, and other factors such as concomitant medications and laboratory indices of anti-coagulation. In all the comparisons, the TIMI criteria for bleeding (CEC adjudicated) were used.

The following summarizes the results of age, gender, ethnicity and weight:

- Major bleeding was not correlated with increasing age, except that the highest incidence was noted in patients >70 years of age in the high dose Integrilin group (7.1%). Minor bleeding was correlated with increasing age in patients treated with Integrilin.
- Patients weighing <74 kg and women had a higher risk of both major and minor bleeding, and this risk was increased in patients treated with Integrilin.
- Patients taking concomitant warfarin and dipyridamole were at increased risk of bleeding, but the risk was not increased by treatment with Integrilin.
- Patients receiving thrombolytics (n=53) had not consistently increased major and minor bleeding with Integrilin treatment.
- Patients with values of ACT over 350 seconds or aPTT over 90 seconds were at increased risk for major bleeding, and the risk was increased by concomitant Integrilin therapy.
- Patients receiving stents were at increased risk for both major and minor bleeding, but the risk was not increased by concomitant Integrilin therapy.
- Patients with early sheath removal (during infusion) experienced less bleeding, although the risk of minor bleeding in this subgroup was higher with concomitant Integrilin.

Summary of Bleeding Adverse Events: There was a small increase in Integrilin-treated patients in minor bleeding according to the TIMI criteria, and in mild and moderate bleeding as reported by the investigators. Major bleeding according to the TIMI criteria and severe bleeding as classified by the investigators were similar in each of the three treatment groups.

Major bleeding occurred most frequently at the femoral artery access site followed by coronary artery bypass related bleeding. Sites most commonly associated with

minor bleeding included the femoral artery access site followed by spontaneous gross hematuria and spontaneous hematemesis.

The majority of investigator-reported bleeding events occurring during or within 24 hours post-infusion termination were mild in severity for all treatment groups. The incidence of severe bleeding events was similar among treatment groups (high dose, 1.0%; low dose, 1.3%; placebo, 0.9%). The excess bleeding events associated with Integrilin compared to placebo were primarily mild, and, to a lesser extent, moderate in severity.

When patients who underwent CABG surgery were excluded, the incidence of major bleeding was lower than in the total population and there were more bleeding events in Integrilin-treated patients (high dose, 2.7% vs. 4.7%; low dose, 2.7% vs. 4.4%; placebo, 1.7% vs. 4.5%, respectively). The incidence of minor bleeding was only slightly less than in the total population. Conversely, the incidence of CABG-related bleeding was highest in the placebo-treated group (2.8% compared to 2.1% and 1.8% in the high and low dose groups respectively).

In all treatment groups, both major and minor bleeding increased with increasing age, decreased weight, in females, and in patients with stents. As expected, the use of warfarin or dipyridamole, as well as an aPTT > 90 seconds increased the incidence of major and minor bleeding in all treatment groups. Early sheath removal decreased the incidence of major and minor bleeding in all treatment groups.

Eighteen patients with underlying renal insufficiency (defined as creatinine > 2.0 mg/dL at baseline) received treatment in this study. Integrilin was not associated with an unusual incidence of bleeding or non-bleeding adverse events.

Overall transfusion requirements were minimally higher in the Integrilin-treated groups (high dose, 5.8%; low dose, 5.5%; placebo, 5.1%), but packed red blood cell and platelet transfusions were not increased among Integrilin-treated patients. The number of transfusions in non-CABG patients was greater in Integrilin-treated than placebo-treated patients (high dose, 4.0%; low dose, 3.5%; placebo, 2.0%). Very few patients required platelet transfusions (0.2% or less).

#### NON-BLEEDING ADVERSE EVENTS

Common adverse events (AE) defined as occurring in  $\geq 2\%$  of patients or with a difference of 0.5% between Integrilin and placebo groups observed within 24 hours and at 30 days of treatment) are summarized in table 8-16 and 8-17.

Three placebo patients died with 30 days of treatment.

In subgroups defined by age, gender and ethnicity, treatment with Integrelin did not result in a clinically relevant increase in non-bleeding AEs compared with placebo. In the 18 patients with serum creatinine > 2 mg/dL, (4 in the high dose, 7 in the low dose Integrelin and 7 in the placebo group) one intracranial bleeding with full recovery occurred in the high dose group.

Integrelin patients with major and minor bleeding had a higher incidence of hypotension and injection site reaction than patients without bleeding events.

**Table 8-16**

**Non-Bleeding Individual Adverse Experiences Occuring Up to 24 Hours Post-Infusion in 2% or More of Treated Patients in Any Treatment Group or with a Difference of 0.5% Between Integrelin and Placebo by Treatment Group**

Body System/Adverse Event	Integrelin High Dose (N=1286)	Integrelin Low Dose (N=1300)	Placebo (N=1285)
Any Non-Bleeding AE	1075 (83.6%) <sup>†</sup>	1069 (82.2%)	1035 (80.5%)
<b>Whole Body</b>			
Back Pain	628 (48.8%)	633 (48.7%)	598 (46.5%)
Headache	165 (12.8%)	152 (11.7%)	181 (14.1%)
Injection Site Reaction	123 (9.6%) <sup>†</sup>	103 (7.9%)	87 (6.8%)
Fever/Chills	108 (8.4%)	82 (6.3%)	102 (7.9%)
Pain	89 (6.9%)	100 (7.7%)	98 (7.6%)
Abdominal Pain	36 (2.8%)	41 (3.2%)	43 (3.3%)
<b>Cardiovascular</b>			
Chest Pain/Angina	344 (26.7%)	357 (27.5%)	359 (27.9%)
Hypotension	275 (21.4%) <sup>†</sup>	241 (18.5%) <sup>†</sup>	192 (14.9%)
Bradycardia	64 (5.0%)	59 (4.5%)	58 (4.5%)
Leg Embolism	15 (1.2%)	11 (0.8%)	8 (0.6%)
Vascular Disorder	10 (0.8%)	14 (1.1%) <sup>†</sup>	5 (0.4%)
Ventricular Fibrillation	9 (0.7%)	5 (0.4%) <sup>†</sup>	14 (1.1%)
Arterial Anomaly	7 (0.5%)	14 (1.1%) <sup>†</sup>	3 (0.2%)
<b>Digestive</b>			
Nausea/Vomiting	277 (21.5%)	275 (21.2%)	268 (20.9%)
Dyspepsia	26 (2.0%)	25 (1.9%)	25 (1.9%)
<b>Hemic and Lymphatic</b>			
Thrombocytopenia	8 (0.6%) <sup>†</sup>	3 (0.2%) <sup>†</sup>	0
<b>Nervous</b>			
Anxiety	34 (2.6%)	31 (2.4%)	35 (2.7%)
Nervous/Agitated	28 (2.2%)	39 (3.0%)	31 (2.4%)
Abnormal Thinking	26 (2.0%)	17 (1.3%)	22 (1.7%)
Insomnia	19 (1.5%) <sup>†</sup>	16 (1.2%)	7 (0.5%)
Paresthesia	18 (1.4%) <sup>†</sup>	7 (0.5%)	7 (0.5%)
Stroke, TIA	9 (0.7%)	6 (0.5%)	3 (0.2%)
<b>Respiratory</b>			
Lung Edema	8 (0.6%)	2 (0.2%) <sup>†</sup>	12 (0.9%)
<b>Urogenital</b>			
Urinary Retention	12 (0.9%)	13 (1.0%)	18 (1.4%)

<sup>†</sup> Events with p<0.05 for likelihood ratio  $\chi^2$  tests of Integrelin vs. placebo

{Source: Summary Table S-47; Summary Listing L-60}

**Table 8-17**  
Non-Bleeding Individual Adverse Events Occurring Within 30 Days of Treatment Initiation in 2% or More of Treated Patients in Any Treatment Group or with a Difference of 0.5% Between Either of the Integrelin-Treated Groups and Placebo by Treatment Group

Body System/Adverse Event	Integrelin High Dose (N=1286)	Integrelin Low Dose (N=1300)	Placebo (N=1285)
Any Non-Bleeding AE	1085 (84.4%)	1090 (83.8%)	1054 (82.0%)
Whole Body			
Back Pain	639 (49.7%)	651 (50.1%)	609 (47.4%)
Headache	199 (15.5%)	186 (14.3%)	205 (16.0%)
Fever/ Chills	143 (11.1%)	113 (8.7%)	132 (10.3%)
Injection Site Reaction	135 (10.5%) <sup>†</sup>	116 (8.9%)	97 (7.5%)
Pain	106 (8.2%)	123 (9.5%)	116 (9.0%)
Abdominal Pain	37 (2.9%)	46 (3.5%)	55 (4.3%)
Allergic Reaction	13 (1.0%)	13 (1.0%)	7 (0.5%)
Cardiovascular			
Chest Pain/Angina	349 (27.1%)	367 (28.2%)	363 (28.2%)
Hypotension	282 (21.9%) <sup>†</sup>	249 (19.2%) <sup>†</sup>	206 (16.0%)
Bradycardia	68 (5.3%)	61 (4.7%)	60 (4.7%)
Atrial Fibrillation	29 (2.3%)	29 (2.2%)	35 (2.7%)
Hypertension	22 (1.7%)	27 (2.1%)	22 (1.7%)
Vascular Disorder	16 (1.2%)	22 (1.7%)	13 (1.0%)
Leg Embolism	18 (1.4%)	12 (0.9%)	12 (0.9%)
Arterial Anomaly	10 (0.8%)	15 (1.2%) <sup>†</sup>	6 (0.5%)
Heart Arrest	10 (0.8%)	6 (0.5%)	13 (1.0%)
Shock	12 (0.9%)	3 (0.2%) <sup>†</sup>	10 (0.8%)
Complete AV Block	7 (0.5%)	2 (0.2%) <sup>†</sup>	9 (0.7%)
Syncope	8 (0.6%) <sup>†</sup>	4 (0.3%)	1 (0.1%)
Ventricular Fibrillation	9 (0.7%)	5 (0.4%) <sup>†</sup>	14 (1.1%)
Digestive			
Nausea/Vomiting	303 (23.6%)	302 (23.2%)	298 (23.2%)
Dyspepsia	32 (2.5%)	29 (2.2%)	30 (2.3%)
Hemic and Lymphatic			
Thrombocytopenia	10 (0.8%) <sup>†</sup>	5 (0.4%)	1 (0.1%)
Metabolic and Nutritional			
Edema	6 (0.5%)	1 (0.1%) <sup>†</sup>	8 (0.6%)
Nervous			
Anxiety	41 (3.2%)	35 (2.7%)	40 (3.1%)
Nervous/Agitated	34 (2.6%)	43 (3.3%)	32 (2.5%)
Abnormal Thinking	31 (2.4%)	23 (1.8%)	33 (2.6%)
Dizziness	29 (2.3%)	23 (1.8%)	25 (1.9%)
Insomnia	23 (1.8%) <sup>†</sup>	18 (1.4%)	10 (0.8%)
Paresthesia	22 (1.7%) <sup>†</sup>	8 (0.6%)	9 (0.7%)
Stroke, TIA	13 (1.0%)	11 (0.8%)	6 (0.5%)
Respiratory			
Lung Edema	11 (0.9%)	6 (0.5%) <sup>†</sup>	17 (1.3%)
Skin			
Rash	13 (1.0%)	8 (0.6%)	5 (0.4%)
Urogenital			
Renal Dysfunction	22 (1.7%)	17 (1.3%)	29 (2.3%)
Urinary Retention	12 (0.9%)	13 (1.0%)	20 (1.6%)

<sup>†</sup> Events with p<0.05 for  $\chi^2$  tests of Integrelin vs. placebo.  
[Source: Summary Table S-48; Summary Listing L-60]

**DEATHS**

The CEC determined the cause of death as cardiovascular (CV), non-CV, and of uncertain etiologies.

A total of 31 patients died within 30 days of randomization. The majority of deaths were from cardiac causes (table 8-22).

**Table 8-22 Deaths Within 30 Days of Randomization by Etiology and Treatment Group**

Cause of Death	High Dose Integrilin (N = 1286)	Low Dose Integrilin (N = 1300)	Placebo (N = 1285)
<b>Total Deaths</b>	11	6	14
<b>Cardiovascular Etiology</b>	8	3	10
MI	6	1	7
CHF	1	0	0
During or Post-CABG	1	0	1
Sudden Death	0	2	2
<b>Non-Cardiovascular</b>	2	3	4
ICH	1	1	0
Medical/Procedural	0	1	4
Other	1	1	0
Uncertain Etiology	1	0	0

A total of 31 patients died between 30 days and 6 months (table 8-24).

**Table 8-24 Patient Deaths from 30 Days Through 6 Months**

CEC Information	High Dose Integrilin (N = 1286)	Low Dose Integrilin (N = 1300)	Placebo (N = 1285)
<b>Total Deaths</b>	10	17	14
<b>Sudden Death</b>	3	7	2
MI	1	4	4
CHF	3	0	1
Medical/Procedural	1	2	2
Other	2	4	5

### ADVERSE EVENTS LEADING TO STUDY DRUG DISCONTINUATION

A total of 178 patients discontinued study drug prior to a 20-hour infusion duration due to an adverse event (table 8-25). The proportion of patients discontinuing study drug prior to a 20-hour infusion due to an adverse event was higher in the Integrilin-treated groups (high dose, 6.1%, low dose, 4.5%) than in the placebo-treated group (3.2%). Study drug discontinuation was primarily due to bleeding which was more common in Integrilin-treated than placebo-treated patients. Bleeding occurred most frequently at the site of femoral artery access in all groups, however, spontaneous bleeding was more frequent in the Integrilin-treated groups.

Coronary occlusion, due to either thrombotic abrupt closure or coronary artery dissection, was less common among the Integrilin groups compared to placebo.

**Table 8-25 Discontinuations Due to Adverse Events by Body System and Treatment Group**

COSTART Preferred Term or Bleeding site +	High Dose Integrilin (N = 1286)	Low Dose Integrilin (N = 1300)	Placebo (N = 1285)
Any Adverse Event	79 (6.1%) †	58 (4.5%)	41 (3.2%)
Bleeding	56 (4.4%) †	46 (3.5%) †	25 (1.9%)
Femoral Artery	33 (2.6%) †	33 (2.5%) †	14 (1.1%)
Multiple sites	12 (0.9%) †	6 (0.5%) †	0
Spont. Hematemesis	6 (0.5%)	3 (0.2%)	4 (0.3%)
Spont. Hematuria	4 (0.3%) †	4 (0.3%) †	0
Whole Body	5 (0.4%)	4 (0.3%)	1 (0.1%)
Cardiovascular	17 (1.3%)	18 (1.4%)	18 (1.4%)
Shock	8 (0.6%)	1 (0.1%)	3 (0.2%)
Coronary Occlusion	4 (0.3%)	2 (0.2%)	9 (0.7%)
Digestive	5 (0.4%) †	3 (0.2%) †	0
Nausea/Vomiting	5 (0.4%) †	3 (0.2%) †	0
Hemic/Lymphatic	4 (0.3%) †	3 (0.2%) †	0
Nervous	6 (0.5%)	4 (0.3%)	3 (0.2%)
Respiratory	2 (0.2%)	1 (0.1%)	1 (0.1%)
Special Senses	1 (0.1%)	0	0
Urogenital	2 (0.2%)	0	0

+ A patient may have had more than one adverse event leading to study drug discontinuation

† P < 0.05 for X<sub>2</sub> test of Integrilin vs. placebo

### SERIOUS ADVERSE EVENTS

Serious adverse events were generally related either to bleeding or to ischemic events. In addition to death and adverse events leading to discontinuation, serious adverse events were evaluated in terms of serious bleeding and non-bleeding events, rehospitalization, strokes.

Serious Bleeding Events Occurring During and Within 24 Hours Post-Infusion Termination (Table 8-27): A total of 202 patients experienced serious bleeding within 24 hours of study drug discontinuation. Patients receiving Integrilin had a higher incidence of serious bleeding than placebo patients (6.1% in the high dose, 5.5% in the low dose, 4.0% in the placebo group). Bleeding at the femoral artery access site accounted for most serious bleeding events and occurred slightly more often in the Integrilin- than placebo-treated patients. CABG-related bleeding and spontaneous hematemesis showed no consistent relationship to treatment. Other serious bleeding events occurred in less than 0.5% of the total population. Intracranial bleeding was uncommon and not more frequent with Integrilin.

Serious Bleeding Events Occurring Within 30-Days of Study Drug Treatment Initiation: A small increase in serious bleeding occurred over 30 days in all groups. The femoral access site accounted for the majority of bleeding events. Bleeding at the femoral artery access site was more frequent in both Integrilin groups than in the placebo group, whereas, CABG-related bleeding was more frequent in the placebo group than in either of the Integrilin groups.

**Table 8-27**  
Incidence of Bleeding at Sites Reported in Treated Patients with Serious Bleeding Complications During Infusion or Within 24 Hours Post-Infusion Termination by Treatment Group

Bleeding Site or COSTART Preferred Term*	Integrilin High Dose (N=1286)	Integrilin Low Dose (N=1300)	Placebo (N=1285)
Any Serious Bleeding Event	78 (6.1%)	72 (5.5%)	62 (4.0%)
<b>Bleeding Location</b>			
Femoral Artery Access Site	55 (4.3%)	54 (4.2%)	34 (2.6%)
CABG Related	10 (0.8%)	9 (0.7%)	13 (1.0%)
Spontaneous Hematemesis	12 (0.9%)	4 (0.3%)	2 (0.2%)
Hct/Hgb Drop Only	4 (0.3%)	4 (0.3%)	5 (0.4%)
Other Sites	2 (0.2%)	6 (0.5%)	6 (0.5%)
Retroperitoneal	3 (0.2%)	4 (0.3%)	0
Spontaneous Gross Hematuria	2 (0.2%)	4 (0.3%)	2 (0.2%)
Oral	4 (0.3%)	2 (0.2%)	0
Other Puncture Site	3 (0.2%)	3 (0.2%)	0
Other Genitourinary	0	3 (0.2%)	1 (0.1%)
Other Gastrointestinal	2 (0.2%)	1 (0.1%)	3 (0.2%)
Intracranial	2 (0.2%)	1 (0.1%)	1 (0.1%)
Hemoptysis	3 (0.2%)	0	2 (0.2%)
Echymoses/Petechiae	2 (0.2%)	1 (0.1%)	0
Epistaxis	1 (0.1%)	0	0

\* A patient may have had more than one bleeding location or bleeding adverse event reported

**Serious Non-Bleeding Events Occurring During Study Drug Administration and Within 30 Days Post-Treatment:** There were 247 serious, non-bleeding adverse events during or within 24 hours after treatment. The incidence of serious non-bleeding adverse events in the Integrilin treatment groups was 7.1% in the high dose, 6.2% in the low dose, and 5.2% in the placebo group. The most common serious non-bleeding adverse events were cardiac related. The only serious non-bleeding event which occurred in greater than 1% in any treatment group was coronary occlusion (high dose 1.3%, low dose 0.9%, placebo 1.3%). The overall incidence of serious adverse events within 30 days of randomization was slightly higher than the 24-hour incidence and similar in type. There was no indication of a delayed effect of treatment or adverse effect of stopping the infusion.

**Rehospitalizations** (table 8-31): Most rehospitalization were due to either angina or diagnostic/interventional coronary procedures and occurred well past the acute period of study drug administration. The incidence of rehospitalization was slightly higher in the Integrilin groups compared with placebo. There was a statistically significant increase in rehospitalization for chest pain/angina in the low dose Integrilin-treated group (6.8%) compared to the placebo-treated group (4.7%).

**Table 8-31**  
Incidence of Reasons for Rehospitalization Reported for 0.5% or More of Treated Patients in Any Treatment Group by Treatment Group

Rehospitalization Reason	Integrilin High Dose (N=1286)	Integrilin Low Dose (N=1300)	Placebo (N=1285)
Rehospitalized	143 (11.1%)	162 (12.5%)	135 (10.5%)
Any Cardiovascular	110 (8.6%)	128 (9.8%)	104 (8.1%)
Coronary Artery Disease	31 (2.4%)	28 (2.2%)	30 (2.3%)
Chest Pain/Angina	66 (5.1%)	88 (6.8%) <sup>†</sup>	60 (4.7%)

<sup>†</sup> P < 0.05 for  $\chi^2$  tests of Integrilin vs. placebo.

**Strokes:** There were 25 CEC-adjudicated strokes, the majority (20) of which were cerebral infarctions. The incidence of cerebral infarction was similar among treatment groups. Primary hemorrhagic stroke occurred in four patients, 2 (0.2%) in the high dose; 1 (0.1%) in the low dose; and 1 (0.1%) in the placebo group. Cerebral infarction with hemorrhagic conversion occurred in one placebo patient. There were 9 additional strokes based only on CRF data, and 3 by CEC-adjudication only. The 9 CRF strokes were all in Integrilin patients (5 high dose, 4 low dose). Of the 3 CEC events, 1 was in the high dose and 2 were in the placebo group. The CEC and investigators did agree on patients with intracranial bleeding; the CEC adjudicated one placebo patient as cerebral infarction with hemorrhagic conversion.

## LABORATORY RESULTS

Except for minor changes in hemoglobin (Hgb) and hematocrit (Hct), the results of laboratory tests did not indicate any adverse effects of Integrilin. Many parameters showed changes from baseline at various time points, but generally the treatment groups did not differ in the magnitude or incidence of these changes.

**Hematologic Parameters:** Decreases in Hgb/Hct between baseline and discharge were slightly greater for Integrilin than placebo patients and consistent with the higher rate of bleeding events in these groups. Mean Hgb levels were similar across treatment groups at baseline, discharge, and Day 30 and were within normal range at all time points. Within each treatment group, mean Hgb levels decreased from baseline to discharge (1.0 to 1.2 g/dL). By Day 30, mean Hgb levels had returned to near baseline levels in all groups.

Decreases in mean Hct paralleled the changes in Hgb in all groups. No clinically meaningful differences were observed among the treatment groups.

The bleeding index (adjusted Hgb change for patients who received transfusions) was calculated prior to determining the TIMI bleeding classification. Mean nadir values for Hgb/Hct, and Bleeding Indices were similar across the treatment groups.

No clinically significant changes in total WBC and differential counts were observed and the three treatment groups showed similar changes from baseline.

Mean platelet counts were similar across treatment groups at baseline and at subsequent time-points. Mean platelet counts remained within normal range at all evaluations. Decreases from mean baseline platelet counts were observed within all treatment groups at most post-baseline evaluations except 30 days. Analysis of changes from baseline to discharge and to Day 30 indicated no statistically significant differences between the treatment groups with respect to degree of change in platelet count. Mean nadir platelet counts were similar in all treatment groups. Less than 1% of patients had platelet counts  $< 50,000/\text{mm}^3$ .

In all treatment groups, more than 85% of patients had normal baseline counts that remained in the normal range. Percentages of patients with platelet counts decreased from normal baseline ranged from 3.2 to 5.2% with no large differences evident among the treatment groups.

ACT  $> 350''$  occurred more frequently than ACT of 300-350'' or  $< 300''$ . More placebo patients had ACT  $< 300''$  and less placebo patients had ACT  $> 350''$ . This differences may be due to the anti-platelet effect of Integrilin.

### Serum Chemistry

**Hepatic Enzymes:** Mean SGPT levels were within normal range (5 to 44 U/L) at baseline and at discharge and were similar across treatment groups at each time point. Mean SGPT was increased at discharge compared to baseline for all treatment groups; these increases were not statistically different across the treatment groups. Between 9.4 and 11.2% of patients with normal baseline SGPT values had values in the high range at discharge; the distribution across treatment groups appears similar. Pairwise comparisons of the incidence of abnormally high SGPT values for Integrilin-treated groups and placebo-treated patients showed no statistically significant differences between groups.

Mean SGOT levels were similar across treatment groups at baseline and discharge and remained within normal range (7 to 41 U/L). Between 8.9% and 11.9% of patients with normal baseline SGOT values had values in the high range at discharge; the distribution across treatment groups appears similar. Pairwise comparisons of SGOT abnormality rates for Integrilin-treated and placebo-treated groups showed no significant differences between groups. There was no evidence of an effect of Integrilin on SGOT.

Mean alkaline phosphatase levels were within normal range (35 to 117 U/L) at baseline and at discharge and were similar across treatment groups at baseline and discharge. Most patients (86.5%) had normal levels at both baseline and discharge. Pairwise comparisons of the incidence of abnormally high alkaline phosphatase values for Integrilin-treated and placebo-treated groups showed no differences between groups.

In summary, there was no evidence of hepatotoxicity by Integrilin in this study in which a large number of patients were evaluated.

**Renal Function Tests:** Mean creatinine levels were 1.1 mg/dL across all treatment groups at baseline and at discharge. Creatinine values for over 90% of patients did not shift into a different range. Proportions of patients with increases in creatinine (normal to high) appeared similar across treatment groups. Similar proportions of patients in the three treatment groups had abnormal post-baseline creatinine values.

Mean BUN levels were similar across treatment groups at baseline and discharge, and remained within normal range of 10-20 mg/dL. No effect of Integrilin on BUN was indicated. Pairwise comparisons between treatment groups showed no significant differences for these changes.

**Cardiac Enzymes:** Cardiac enzyme measurements (CK, CK-MB) were included in this study for determination of efficacy outcomes.

At baseline, mean and median CK were highest in the high dose Integrilin-treated group, followed by the placebo-treated group and the low dose Integrilin-treated group. At all subsequent time points, CK was highest in the placebo-treated group, and changes from baseline mean in CK were larger in the placebo-treated group than in the Integrilin-treated groups. Pairwise comparisons showed no statistically significant differences in mean change from baseline to 24 hours.

The proportion of patients that had a post-baseline CK  $> 3 \times$  ULN or  $> 3 \times$  baseline in the placebo group (6.5%) was statistically greater than the proportions of patients in the low dose (4.3%) or high dose (4.1%) Integrilin groups.

The smaller changes from baseline in CK observed in the Integrilin groups, as well as the significantly smaller percentage of Integrilin patients having CK  $> 3 \times$  ULN (defined in protocol as evidence of MI) compared to placebo are consistent with an effect of Integrilin on MI. This parameter was used by the CEC to ascertain MI occurrence per protocol.

Mean CK-MB was highest in the high dose group at baseline (10.8 ng/mL) followed by the low dose group (7.5 ng/mL) and the placebo group (6.2 ng/mL). At all subsequent evaluations, mean CK-MB levels were higher than at baseline except for the low dose Integrilin group at 24 hours. The greatest changes in CK-MB were in the placebo group, with significant increases within the placebo group from baseline to 6, 12 and 24 hours. No significant changes from baseline CK-MB were detected in either of the Integrilin treatment groups. Pairwise comparisons between treatment groups showed no significant differences in CK-MB change from baseline to 24 hours.

**Laboratory Analysis Conclusions:** Overall, examination of results of laboratory tests did not indicate adverse effects of Integrilin, with the exception of minor changes in hemoglobin and hematocrit.

## CONCLUSIONS

IMPACT II study was a randomized, double-blind, multicenter study of 4010 patients enrolled at 83 centers. The study adequately represented a cross section of the target population. Two dose regimens of Integrilin consisting of a common bolus dose of 135 ug/kg followed by a 20-24 hour infusion of either 0.5 or 0.75 ug/kg/min were compared to placebo. All patients received aspirin and heparin. The three treatment groups were well balanced for demographic characteristics, cardiovascular history and clinical presentation.

The primary efficacy endpoint was represented by the composite of death, MI, and need for urgent revascularization (as determined by the CEC) occurring within 30 days from randomization. Secondary endpoints included the incidence of abrupt closure, clinical events at 6 months, effect of subgroup factors, proportion of patients with successful angioplasty, proportion of patients receiving thrombolytics and incidence of cardiac mortality.

The treated population was selected for primary efficacy analysis rather than the randomized population because some patients were randomized before eligibility could be determined and before the decision to proceed with angioplasty was made by the investigator. Consequently, some patients were never treated. The decision not to treat the patient was made by the investigator blinded to potential treatment assignment. The number of untreated patients and the reasons for omitting treatment were evenly distributed among the three treatment groups. The efficacy analysis was, however, performed on the randomized population as well to check for possible bias.

Statistical significance was determined as two-sided Type 1 error at alpha value of 0.035 for multiple comparisons adjustment. The estimated p-value of 0.035 actually corresponded to an adjusted p-value of 0.067 rather than 0.05.

A reduction in the incidence of the CEC adjudicated composite endpoint of death, MI and/or the need for urgent intervention after coronary angioplasty was observed in patients treated with Integrilin. The Integrilin effect was realized with both dose regimens during and shortly after the index angioplasty. At 24 hours post-randomization, statistically significant reductions in composite endpoint and in revascularization procedures were observed in both Integrilin treatment arms compared to placebo and in both treated and randomized population analyses. At 48 hours post-randomization, the difference between Integrilin groups and placebo was statistically significant in the treated population analysis.

The incidence of abrupt closure was significantly reduced in both Integrilin groups compared to placebo. This reduction was consistent with the significant reduction in ischemic events observed during the period of drug administration and up to 48 hours period of observation.

At the primary endpoint analysis at 30 days, the statistically significant benefit for the composite endpoint and for urgent CABG was maintained only in the low-dose Integrilin group compared to placebo in the treated population analysis. Post-hoc analysis of the combined Integrilin groups compared to placebo for the 30 day composite endpoint showed a numerical difference in the treated population analysis (p-value <0.05 but >0.035) .

A numerical decrease (not statistically significant) of in the components of death and myocardial infarction in the Integrilin-treated groups was still present at 6 months after enrollment.

Compared to placebo, both Integrilin groups showed a numerically lower incidence of the CEC adjudicated composite endpoint and of each of its components in every analyses and at all time periods.

Efficacy analysis was also performed based on the investigator-determined clinical endpoint events. By this analysis, statistically significant reductions in incidence of composite endpoint and urgent CABG were observed in the Integrilin low-dose group compared to placebo in both randomized and treated population analyses. The frequency of investigator-reported events was lower than adjudicated by the CEC, particularly for incidence of MIs. Approximately one third of the CEC-adjudicated MI were also reported by the investigators. The discrepancy was due to the fact that the CEC identified post-angioplasty MIs on the basis of increased CK and CK/CK-MB levels. Nevertheless, nearly one half of the CEC-adjudicated large enzyme MIs were not reported (or diagnosed) by the investigators. There was no imbalance in the relative distribution of MIs in the three treatment groups by the investigators and by the CEC. No significant imbalance was noted for the reports of MIs or composite end point among study centers.

Subgroup analyses revealed that the patients most likely to benefit from Integrilin therapy were those presenting for elective angioplasty. However, it must be noted that the incidence rates of events observed for high risk and low risk patients (as determined in the CRFs) were similar in the placebo group, therefore, the criteria used for risk identification were not predictive of outcome.

Subgroup analyses also showed greater benefit from Integrilin in patients weighing

75 kg or more, and those receiving a stent during the procedure.

Integrilin was shown to be safe in both regimens studied. Bleeding events were the most common adverse events that appeared to be related to Integrilin therapy. Incidences of the most serious bleeding events, including major (according to the TIMI criteria) and severe bleeding (as assessed by the Principal Investigators), and the incidence of red blood cell transfusions were similar in both Integrilin treated groups and in the placebo group.

However, less clinically serious bleeding events, including minor, mild and moderate bleeding and study drug discontinuations due to bleeding were more common in Integrilin-treated patients, particularly in the high dose group. Furthermore, among the serious adverse events, bleeding events were more frequent in the integrilin groups than in the placebo groups, and study drug discontinuation because of bleeding occurred more frequently in the Integrilin groups than in the placebo group.

Non-bleeding adverse events that were increased in Integrilin treated patients compared to the placebo group included back pain, hypotension and discomfort at the vascular access site. Hypotension and discomfort at the vascular access site were more common in patients with bleeding events.

No new or unexpected adverse events were reported from the large study population of 2586 patients treated with Integrilin in the IMPACT II clinical trial.

No laboratory abnormalities were associated with Integrilin therapy.

No effect of Integrilin on hepatic or renal function were noted. No increased incidence of thrombocytopenia was reported for the Integrilin groups compared to placebo.

The plasma levels of Integrilin and the distribution of estimated C<sub>ss</sub> in IMPACT II suggests that only 44.5% of the patients in the 0.50 mg/kg-min group and only 68.3% of the patients in the 0.75 mg/kg-min group had a steady-state plasma concentration, which would have resulted in at least 80% inhibition of ADP-induced *ex vivo* platelet aggregation, based on the IC<sub>80</sub> estimate of 292 ng/mL obtained in Study 93-012.

No Integrilin antibodies were detected in 425 patients tested.

## INTEGRATED SUMMARY OF EFFICACY (ISE)

### Data Sets Analyzed:

- Studies in Coronary Angioplasty
- Studies in Unstable Angina

The total study population included in the ISE consists of 4525 patients. Of these, 4206 or 92.9% were Coronary Angioplasty patients and 319 were patients with Unstable Angina (UA) or Non-Q-Wave Myocardial Infarction (NQMI).

A total of 4010 of the 4206 coronary angioplasty patients (95.3%) were randomized in study IMPACT II. Therefore, the ISE is derived primarily from the data from IMPACT II which have been described in details in the study review.

### STUDIES IN CORONARY ANGIOPLASTY:

Three Phase II/III clinical trials were conducted with Integrilin in patients undergoing PTCA. The first study (IMPACT I, Protocol 92-009) was a randomized, multi-center, double-blind study conducted at 15 centers. This study examined 150 patients and compared two dosing regimens of Integrilin, specifically one common dose of Integrilin and two infusion of different durations, to placebo treatment in patients during and after coronary angioplasty.

The second study (IMPACT High/Low) was conducted at 4 centers to determine the pharmacokinetics and pharmacodynamics of various dosing regimens of Integrilin, as assessed by Integrilin plasma concentrations, inhibition of *ex vivo* ADP-induced platelet aggregation, and bleeding time. Information obtained from this study of 73 patients was used to select the dosing regimens for the Phase III pivotal study (IMPACT II: Integrilin to Manage Platelet Aggregation and prevent Coronary Thrombosis).

The IMPACT II clinical trial was a large, double-blind, multi-center study which examined the use of Integrilin in patients undergoing coronary angioplasty (balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty or excimer laser angioplasty [PTCA]). The trial included 4010 patients and was carried out at 82 centers in the U.S..

A total of 139/4010 (3.5%) randomized patients, similarly distributed among the treatment groups, were not treated with study medication. This was due to the fact that many patients were enrolled before the final decision was made to proceed to angioplasty.

Two dosing regimens of Integrelin were each compared to placebo. The primary efficacy endpoint for the study was the composite occurrence of death, myocardial infarction and/or urgent coronary intervention.

Two methods of assessment of the composite endpoint, that of the Clinical Events Committee (CEC) and that of the Principal Investigators, were employed to investigate clinical efficacy and safety. The CEC was independent and blinded to study treatment. The CEC assessed all patients at all sites, thus eliminating individual investigator bias.

Table 2-1 outlines the number of patients included in each of the populations studied in the three clinical trials of Integrelin. The Impact II study contributes approximately 95% of the patient population included in the ISE.

**Table 2-1**  
Summary of Number of Subjects Included in Randomized  
and Treated Patient Populations

Study	Integrelin		Placebo	
	All Randomized	All Treated	All Randomized	All Treated
IMPACT II	2682	2586	1328	1285
IMPACT I	101	98	49	46
IMPACT High/Low	54	52	19	17
<b>Total</b>	<b>2837</b>	<b>2736</b>	<b>1396</b>	<b>1348</b>

**Pooled Efficacy Analysis (IMPACT I and IMPACT II):** The results of the two studies are analyzed jointly because the initial IMPACT I and IMPACT II employed a similar endpoint - death, MI, and/or urgent intervention, both studies followed patients to 30 days and the component events were adjudicated under blinded conditions.

The regimens employed in the initial IMPACT and IMPACT II studies were different. IMPACT used a common bolus of 90 mg/kg and a continuous infusion of 1.0 mg/kg-min for either of two different durations (4 or 12 hours). IMPACT II used a common bolus of 135 mg/kg and two different rates of continuous infusion (0.50 or 0.75 mg/kg-min) for 20-24 hours.

Since there is no overlap of the regimens employed in the two studies, the pooled Integrelin patients were compared to the pooled placebo patients.

Table 2-15 illustrates the incidence of the composite endpoint at 30 days used to calculate the pooled analysis, using the entire treated patient population from each trial.

**Table 2-15 Number of Patients with the Composite Endpoint at 30 Days - Combined Analysis, IMPACT and IMPACT II -Treated Patients**

	Integrilin (n = 2684)	Placebo (n = 1331)
Patients with Composite Endpoints	253 (9.4%)	154 (11.6%)
% Reduction	18.9%	---
Chi Square Test $p = 0.036$		
OR = 0.795 ; 95% CI (0.643-0.983)		

The majority of the clinical effect occurred during the period of administration, however, the absolute benefit accrued by patients receiving Integrilin remained after 30 days.

No withdrawal or rebound effect after cessation of therapy were observed.

#### STUDIES IN UNSTABLE ANGINA/NON Q-WAVE MYOCARDIAL INFARCTION

The effectiveness of Integrilin in limiting the ischemic manifestations and symptoms of UA/NQMI has been evaluated in three completed phase II studies involving a total of 319 based on predetermined criteria. A large Phase III study (PURSUIT) is presently ongoing.

The three completed Phase II studies in UA/NQWMI are summarized as follows:

**Study 91-007:** A randomized, double-blind comparative safety and efficacy evaluation of Integrilin versus aspirin in the management of unstable angina

A total of 227 patients with recent onset of increasingly intense anginal pain accompanied by either ST segment/T wave changes on the ECG, or a history of previous MI or cardiac catheterization and the use of anti-ischemic medication were randomized, and 223 patients were treated. Patients were randomized into one of three treatment groups consisting of Integrilin High Dose, Integrilin Low Dose and placebo. The patients received a bolus dose followed by a continuous Integrilin or placebo infusion for 24-72 hours. All patients received heparin.

Based on results from the high dose group, Integrilin resulted in a 31% reduction compared to aspirin in the proportion of patients who had Holter-defined ischemic events, a 31% reduction in the number of events per patient, and a 21% reduction in the overall duration of these events. Among patients with symptomatic ischemia, there was a 28% reduction compared to aspirin in the number of events per patient, and a 31% reduction in the total duration of such events. These results

suggest a treatment effect of Integrilin in patients with unstable angina.

Study 92-010: A randomized, double-blind comparative safety and efficacy evaluation of Integrilin alone versus heparin/aspirin in the management of UA.

This study consisted of two parts: a pilot study and a main study. In the pilot study, 12 patients with chronic stable angina were treated with Integrilin (90 mg/kg bolus followed by a 1.0 mg/kg-min infusion for 6 hours or a 135 mg/kg bolus followed by a 1.5 mg/kg-min infusion for 6 hours) to determine the dosing regimen for the main study. In the main, double-blind study, 14 patients with UA were treated with aspirin plus heparin, and 16 patients were treated with Integrilin alone as a bolus of 135 mg/kg followed by a continuous infusion of 1.5 mg/kg-min for 48 to 56 hours. Patients receiving Integrilin alone were not to receive heparin or ASA. Holter-defined ischemic events were infrequent in this study and precluded any meaningful comparison between treatments, however, the data for symptomatic ischemia suggested a therapeutic advantage for Integrilin. Episodes of symptomatic ischemia were more common (56% vs 31% of patients) and of longer duration (28.4 min vs 8.4 min) among patients treated with aspirin plus heparin than with Integrilin alone.

Study 92-015: A randomized, open-label comparative safety and efficacy evaluation of Integrilin alone versus heparin plus aspirin in the management of unstable angina (IMPACT USA)

This study was an open-label study in which various dose regimens of Integrilin (120 mg/kg + 1.0 mg/kg-min, 135 mg/kg + 1.0 mg/kg-min, and 150 mg/kg + 1.25 mg/kg-min, either with or without heparin) were compared to heparin plus aspirin and a placebo Integrilin infusion (the control group) in patients with UA/NQMI. A total of 61 patients were randomized and 57 were treated including approximately 6 to 8 patients for each of the various Integrilin combinations and 18 patients in the control group. Infusions were to be continuous and last for 12 to 72 hours.

The sample sizes in this study preclude any meaningful comparison of treatment groups or a definitive dose-response analysis, however, symptomatic ischemia was reported in 33% (6/18) of patients in the control group and in 23% (9/39) of patients who received Integrilin.

In summary, the results of these studies suggest that Integrilin limits both symptomatic and Holter-defined ischemia in these patients, based on an analysis of the number of patients with ischemic events, the number of events per patient, and the duration of these events.

### **INTEGRATED SUMMARY OF SAFETY (ISS)**

The overall clinical program of Integrilin includes a total of 4888 subjects enrolled in 14 completed clinical studies including:

- three studies in patients undergoing coronary angioplasty: two Phase II studies (the IMPACT I and the IMPACT High/Low study) and one large Phase III study (the IMPACT II study).
- three completed Phase II studies conducted in patients with unstable angina/non Q-wave MI (UA/NQMI). One of the Phase II studies also included a pilot study in patients with stable angina.
- five Phase I studies conducted in healthy volunteers
- an immunogenicity study (94-019) in healthy volunteers
- a study (94-020) in renal impaired subjects
- a Phase II study (92-011) in patients with acute myocardial infarction (AMI)
- one patient was administered Integrilin under an emergency IND.

One additional, large Phase III clinical trial of Integrilin in patients with UA/NQMI (94-016 or PURSUIT) is presently ongoing.

A total of 4888 subjects was enrolled in the completed studies and a total of 4722 received the assigned treatment. Of the treated patients, 3176 were exposed to Integrilin.

The ISS database in the NDA is derived from the three studies of Integrilin as adjunctive therapy to coronary angioplasty (PTCA) and from the three studies in Unstable Angina/Non Q-Wave Myocardial Infarction (UA/NQMI) since patients with UA/NQMI represent a subset of patients undergoing PTCA.

These six studies are integrated into one pooled database and tabulations are presented on the entire ISS database. Because of demographic and dose differences between the two patient populations (i.e., the coronary angioplasty patient population and the UA/NQMI patient population) separate analyses and comparisons within the ISS database are performed when appropriate.

A total of 4394 patients in the ISS database actually received treatment with either Integrilin (2939) or a matching placebo (1455). At least 88% of the ISS database is represented by the IMPACT II study.

Data from studies not included in the ISS database (Clinical Pharmacology studies) are discussed separately.

This ISS includes adequate information to characterize the safety of Integrilin and to conclude that Integrilin, at the dose regimen used in the studies, has an acceptable safety profile.

The distribution of patients in the 14 completed studies is summarized in Table 2-3.

**Table 2-3**  
Distribution of Enrolled and Treated Subjects Among Studies

	Enrolled			Treated		
	Integrelin	Control	Total	Integrelin	Control	Total
<b>PATIENTS</b>						
<b>PTCA</b>						
Study 92-009	101	49	150	98	46	144
Study 93-012	54	19	73	52	17	69
Study 93-014	2682	1328	4010	2586	1285	3871
Subtotal	2837	1396	4233	2736	1348	4084
<b>UNSTABLE ANGINA</b>						
Study 91-007B	153	74	227	150	73	223
Study 92-010A*	14	17	31	14	16	30
Study 93-015	41	20	61	39	18	57
Subtotal	208	111	319	203	107	310
ISS Database	3045	1507	4552	2939	1455	4394
<b>VOLUNTEERS</b>						
Study 91-001	17	8	25	17	8	25
Study 91-002	28	14	42	28	14	42
Study 91-004	11	4	15	10	4	14
Study 91-006	9	5	14	8	4	12
Study 92-008	4	0	4	4	0	4
Subtotal	69	31	100	67	30	97
<b>OTHER STUDIES</b>						
Study 92-010*	12	0	12	12	0	12
Study 92-011**	125	55	180	121	54	175
Study 94-019	21	7	28	21	7	28
Study 94-020	16	0	16	16	0	16
Subtotal	174	62	236	170	61	231
<b>TOTAL SUBJECTS</b>						
All Studies	3288	1600	4888	3176	1546	4722

\* One study with two separate patient populations.

\*\* Database not finalized by November 30, 1995

**Analyses of Adverse Events:** In the ISS Database, adverse events were defined as occurring before study treatment, during treatment or within 24 hours post-treatment, and after 24 hours post-treatment.

Adverse events were classified as either non-bleeding or bleeding.

Non-bleeding adverse events were coded using COSTART and data were compared overall and by COSTART body system and by treatment group. Adverse events were analyzed by the following variables: indication; gender; ethnicity; age (< 60, = > 60); weight by gender interactions; cumulative dose; hypertension at baseline; diabetes at baseline; cerebrovascular disease at baseline; peripheral vascular disease at baseline; onset of adverse event at pretreatment, during treatment, end of treatment to 24 hours and after 24 hours post-treatment; and severity.

Data on the site and severity of any bleeding event occurring during the Integrilin infusion or shortly after terminating the infusion were collected and analyzed separately. Bleeding was characterized in three ways:

- 1) TIMI criteria which included:
  - a. Major Bleeding (Intracranial bleeding or bleeding associated with a decrease in Hgb or Hct greater than 5 g/dL or 15%;
  - b. Minor Bleeding (spontaneous gross hematuria or hematemesis, or blood loss with Hgb decrease > 3 g/dL and < 5 g/dL, or a decrease in Hgb > 4 g/dL and < 5 g/dL with no bleeding site identified); and,
  - c. Insignificant Bleeding (blood loss insufficient to meet criteria for minor bleeding).
- 2) Investigator assessment, which included:
  - a. Severe,
  - b. Moderate, and
  - c. Mild bleeding,
- 3) Need for transfusions.

The mean and median change from baseline in each hematology, serum chemistry, and urinalysis parameter were summarized. For each parameter, treatment with Integrilin was compared to placebo to identify changes from baseline potentially associated with treatment with Integrilin. Patients with marked abnormalities in laboratory parameters as defined in study protocols were also identified.

**Statistical Analyses of Adverse Events:** For each analysis of adverse events with an occurrence of 1% or greater in any treatment group, an extended Cochran-Mantel-Haenszel (CMH) chi-square ( $\chi^2$ ) test statistic was calculated comparing Integrilin-treated patients to placebo patients. For strata in categories, a CMH General Association (GA) test statistic was used to evaluate differential incidence of adverse events between Integrilin and placebo across the strata and a Breslow-

Day test of Homogeneity of Odds Ratio was calculated to test the homogeneity of the treatment effect among strata. For strata with more than two categories and an ordinal ranking (i.e., cumulative dose), a CMH ANOVA test statistic with non-parametric scores (modified ridit scores) was calculated.

## RESULTS OF ISS

The sections addressed in this ISS are as follows:

- 1.0 Demographics (age, gender, race, and pre-existing diseases), and differences among subgroups in response to Integrilin.
- 2.0 Extent of exposure to Integrilin (length of exposure and total cumulative dose)
- 3.0 Adverse events (all adverse events, common adverse events, with separate discussion of bleeding events). All deaths and discontinuations due to adverse events.
- 4.0 Laboratory evaluations (changes in laboratory parameters that may indicate underlying safety issues).
- 5.0 Analyses of drug-drug interactions, drug-disease interactions, and drug-demographics interactions.
- 6.0 Dosing considerations and relation to adverse effects.
- 7.0 Safety Update (4 month)

### 1.0 Demographics

The demographics of the patients included in the integrated safety analysis were consistent with those expected in this patient population. The overall ISS database, 93% of which was made up of coronary angioplasty patients, was predominantly Caucasian (91%), male (74%), and greater than 50 years old (82%). Fifty-five percent of the patients had a history of hypertension and 23% had a diagnosis of diabetes. Very few patients had a history of cerebrovascular disease (2.2%), a designation that included a TIA or a previous stroke, while 6.5% of the patients had peripheral vascular disease, primarily diagnosed as intermittent claudication.

The 319 patients from the three studies in UA/NQMI represented only 7% of the ISS database, however, the demographics of the patients enrolled in the studies of Integrilin in the treatment of UA/NQMI were different from the patients enrolled in the coronary angioplasty studies. In general, the patients with unstable angina were older and there were higher proportions of black and female patients than in the studies in coronary angioplasty.

The demographic data by indication and by treatment are summarized in table 4-1

**Table 4-1**  
**Demographics by Indication and Treatment Group**

Demographic Characteristic	Coronary Angioplasty Studies			Unstable Angina Studies			Total		
	Integrelin	Placebo	Total	Integrelin	Placebo	Total	Integrelin	Placebo	Total
<b>Gender</b>									
Male	2045 (74.7%)	1018 (75.5%)	3063 (75.0%)	118 (58.1%)	69 (64.5%)	187 (60.3%)	2163 (73.6%)	1087 (74.7%)	3250 (74.0%)
Female	691 (25.3%)	330 (24.5%)	1021 (25.0%)	85 (41.9%)	38 (35.5%)	123 (39.7%)	776 (26.4%)	368 (25.3%)	1144 (26.0%)
Total	2736	1348	4084	203	107	310	2939	1455	4394
<b>Ethnicity</b>									
Caucasian	2516 (92.1%)	1217 (90.4%)	3733 (91.6%)	31 (79.5%)	11 (61.1%)	42 (73.7%)	2547 (91.9%)	1228 (90.0%)	3775 (91.3%)
Black	111 (4.1%)	75 (5.6%)	186 (4.6%)	7 (17.9%)	5 (27.8%)	12 (21.1%)	118 (4.3%)	80 (5.9%)	198 (4.8%)
Asian	6 (0.2%)	4 (0.3%)	10 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.2%)	4 (0.3%)	10 (0.2%)
Hispanic	69 (2.5%)	41 (3.0%)	110 (2.7%)	1 (2.6%)	2 (11.1%)	3 (5.3%)	70 (2.5%)	43 (3.2%)	113 (2.7%)
Other	29 (1.1%)	9 (0.7%)	38 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (1.0%)	9 (0.7%)	38 (0.9%)
Total	2731	1346	4077	164	89	253	2770	1364	4134
Missing	5	2	7	39	18	57	169	91	260
<b>Age</b>									
20-29	2 (0.1%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (0.1%)	3 (0.1%)
30-39	84 (3.1%)	30 (2.2%)	114 (2.8%)	5 (2.5%)	6 (5.6%)	11 (3.5%)	89 (3.0%)	36 (2.5%)	125 (2.8%)
40-49	426 (15.6%)	225 (16.7%)	651 (15.9%)	20 (9.9%)	11 (10.3%)	31 (10.0%)	446 (15.2%)	236 (16.2%)	682 (15.5%)
50-59	801 (29.3%)	416 (30.9%)	1217 (29.8%)	53 (26.1%)	24 (22.4%)	77 (24.8%)	854 (29.1%)	440 (30.2%)	1294 (29.4%)
60-69	859 (31.4%)	409 (30.3%)	1268 (31.0%)	63 (31.0%)	38 (35.5%)	101 (32.6%)	922 (31.4%)	447 (30.7%)	1369 (31.2%)
≥70	564 (20.6%)	267 (19.8%)	831 (20.3%)	62 (30.5%)	28 (26.2%)	90 (29.0%)	626 (21.3%)	295 (20.3%)	921 (21.0%)
Total	2736	1348	4084	203	107	310	2939	1455	4394
<b>Age</b>									
N	2736	1348	4084	203	107	310	2939	1455	4394
Mean	59.7	59.8	59.7	62.4	61.4	62.1	59.9	59.7	59.8
SD	10.76	10.75	10.76	10.37	10.97	10.58	10.75	10.77	10.76

**Table 4-1 (Cont)**  
**Demographics by Indication and Treatment Group**

Demographic Characteristic	Coronary Angioplasty Studies			Unstable Angina Studies			Total		
	Integrelin	Placebo	Total	Integrelin	Placebo	Total	Integrelin	Placebo	Total
<b>Hypertension</b>									
No	1245 (45.6%)	611 (45.4%)	1856 (45.5%)	73 (36.0%)	43 (40.2%)	116 (37.4%)	1318 (44.9%)	654 (45.0%)	1972 (44.9%)
Yes	1487 (54.4%)	735 (54.6%)	2222 (54.5%)	130 (64.0%)	64 (59.8%)	194 (62.6%)	1617 (55.1%)	799 (55.0%)	2416 (55.1%)
Total	2732	1346	4078	203	107	310	2935	1453	4388
Missing	4	2	6				4	2	6
<b>Diabetes</b>									
No	2109 (77.1%)	1042 (77.5%)	3151 (77.2%)	147 (72.4%)	75 (70.1%)	222 (71.6%)	2256 (76.6%)	1117 (76.9%)	3373 (76.9%)
Yes	625 (22.9%)	303 (22.5%)	928 (22.8%)	56 (27.6%)	32 (29.9%)	88 (28.4%)	681 (23.2%)	335 (23.1%)	1016 (23.1%)
Total	2734	1345	4079	203	107	310	2937	1452	4389
Missing	2	3	5				2	3	5
<b>Cerebral Vascular Disease</b>									
No	2682 (98.1%)	1318 (98.0%)	4000 (98.1%)	191 (94.1%)	100 (93.5%)	291 (93.9%)	2873 (97.9%)	1418 (97.7%)	4291 (97.8%)
Yes	51 (1.9%)	27 (2.0%)	78 (1.9%)	12 (5.9%)	7 (6.5%)	19 (6.1%)	63 (2.1%)	34 (2.3%)	97 (2.2%)
Total	2733	1345	4078	203	107	310	2936	1452	4388
Missing	3	3	6				3	3	6
<b>Peripheral Vascular Disease</b>									
No	2558 (93.6%)	1257 (93.7%)	3815 (93.6%)	185 (91.1%)	99 (92.5%)	284 (91.6%)	2743 (93.5%)	1356 (93.6%)	4099 (93.5%)
Yes	174 (6.4%)	85 (6.3%)	259 (6.4%)	18 (8.9%)	8 (7.5%)	26 (8.4%)	192 (6.5%)	93 (6.4%)	285 (6.5%)
Total	2732	1342	4074	203	107	310	2935	1449	4384
Missing	4	6	10				4	6	10

## 2.0 Extent of Exposure

Dosing information was not available on 66 of the 2939 patients treated with Integrilin. The majority of the patients (64/66) without Integrilin dosing information were enrolled in IMPACT II study. The remaining two patients without dosing information were in IMPACT I study.

The extent of exposure to study treatments was characterized in two ways: cumulative dose (divided into  $\leq 700$ , 700-850, 850-1000, 1000-1150, and  $\geq 1150$  ug/kg) and duration of exposure (divided into  $\leq 12$ , 12-24, 24-48, and  $\geq 48$  hours).

**2.1 Cumulative Dose:** In the studies of patients undergoing coronary angioplasty, 30% of the patients received a cumulative dose commensurate with the expected dosing recommendations in the proposed package insert (735-855 ug/kg) and 56% of patients received cumulative doses in excess of the dosage regimen in the proposed package insert. The majority (61%) of patients received cumulative Integrilin doses of less than 1000 ug/kg.

The majority of patients (79%) enrolled in the studies of Integrilin for treatment of UA/NQMI have received Integrilin doses greater than 1000 ug/kg.

The demographic distribution examined by cumulative dose categories did not show any obvious imbalances in treatment.

**2.2 Duration of Exposure:** Depending on the study and the indication, the protocol defined duration of Integrilin infusion varied from 4 hours up to 72 hours. For studies of patients undergoing coronary angioplasty, the majority of the patients were exposed to Integrilin for a period of time consistent with that expected dosage recommendations in the proposal package insert (i.e., 20-24 hours).

The majority of patients in the ISS database (77%) received an Integrilin infusion lasting between 12 and 24 hours. Approximately 13% of patients in the ISS database treated with Integrilin have received infusions lasting longer than 24 hours. Another 10% of patients treated with Integrilin have received infusion lasting less than 12 hours.

The patients who received an infusion of Integrilin for greater than 48 hours (n=48) were all in the UA/NQMI studies. In this group, 48% were females compared with approximately 26% of females in the overall ISS database, and 48% was over the age of 70 compared to 21% in the overall population.

A summary of the cumulative doses of Integrilin is provided in table 5-1. The duration of exposure to Integrilin by study is summarized in table 5-3.

**Table 5-1**  
Total Cumulative Dose by Study\*

		Total Cumulative Dose (µg/kg)										Total	
		≤ 700		700 - 850		850 - 1000		1000 - 1150		≥ 1150			
		N	%	N	%	N	%	N	%	N	%	N	%
Coronary Angioplasty Studies	92-009	58	60.4	10	10.4	26	27.1	1	1.0	1	1.0	96	100
	93-012	11	21.2	8	15.4	12	23.1	9	17.3	12	23.1	52	100
	93-014	313	12.4	817	32.4	383	15.2	553	21.9	456	18.1	2522	100
	Total	382	14.3	835	31.3	421	15.8	563	21.1	469	17.6	2670	100
UA/NQMI Studies	91-007B	13	8.7	25	16.7	0	0	3	2	109	72.7	150	100
	92-010A	1	7.1	0	0	0	0	0	0	13	92.9	14	100
	93-015	1	2.6	0	0	3	7.7	7	17.9	28	71.8	39	100
	Total	15	7.4	25	12.3	3	1.5	10	4.9	150	73.9	203	100
All Studies		397	13.8	860	29.9	424	14.8	573	19.9	619	21.5	2873	100

\*Patients with Integrelin dose information only

**Table 5-3**  
Duration of Exposure (hours) to Integrelin by Study\*

		Duration of Exposure (hrs)								Any Exposure	
		≤12		12-24		24-48		≥48			
		N	%	N	%	N	%	N	%	N	%
Coronary Angioplasty Studies	92-009	58	60.8	37	38.1	1	1.0	0	0.0	96	100.0
	93-012	6	11.5	42	80.8	4	7.7	0	0.0	52	100.0
	93-014	209	8.3	2063	81.8	250	9.9	0	0.0	2522	100.0
	Total	273	10.2	2142	80.2	255	9.6	0	0.0	2670	100.0
Unstable Angina Studies	91-007B	6	4.0	42	28.0	64	42.7	38	25.3	150	100.0
	92-010A	1	7.1	1	7.1	6	42.9	6	42.9	14	100.0
	93-015	2	5.1	28	71.8	5	12.8	4	10.3	39	100.0
	Total	9	4.4	71	35.0	75	36.9	48	23.6	203	100.0
All Studies		282	9.9	2213	77.0	330	11.5	48	1.7	2873	100.0

\*Patients with Integrelin dose information only

### 3.0 Adverse Events

3.1 Adverse Events in ISS Database: Overall, there was twice the frequency of adverse event reporting in the patients undergoing coronary angioplasty than in patients with UA/NQMI. This was related to three factors:

- 1).The inclusion of adverse events potentially attributable to the angioplasty procedure, such as the insertion of arterial catheters and the effects of the use of angioplasty devices;
- 2).The difference in data collection methods (primarily spontaneous reporting versus elicited adverse events in the large IMPACT II study); and
- 3).The duration of observation (30 days in coronary angioplasty versus 24 hours post-treatment/hospital discharge in UA/NQMI studies).

As 95% of the coronary angioplasty patients in the ISS database were from the IMPACT II study, the integrated safety results in these patients do not differ significantly from the results of the IMPACT II study.

### 3.2 Safety Results in Healthy Volunteer Subjects Not in the ISS Database :

Adverse events reported in the five Phase I studies in healthy human volunteers were rare. The overall incidence of any event was 64.2% in the Integrilin group compared to 70% in the placebo group. No severe or life-threatening events were reported. The most common adverse event in volunteers receiving Integrilin was bleeding at an injection site.

There were no clinically significant trends in laboratory test results.

3.3 Bleeding Events in Phase II and Phase III Studies: Bleeding was evaluated using three sets of criteria: TIMI criteria (using both laboratory and clinical data); frequency and severity of investigator-reported bleeding events, and incidence of transfusion of red blood cells, platelets or plasma

3.3.1 Bleeding According to TIMI Criteria: The overall incidence of major bleeding events was low and was similar in the Integrilin group and the placebo group. Patients undergoing angioplasty had a higher rate of major bleeding events due to the invasive procedure than did patients with UA/NQMI.

Overall the incidence rates of minor and insignificant bleeding events were higher among Integrilin-treated patients compared to placebo-treated patients, mainly in patients undergoing PTCA compared to the patients with UA/NQMI.

The most common site of major bleeding was the femoral artery access site and CABG related bleeding. The distribution of sites of bleeding events was similar between treatment groups.

The incidence of bleeding in the overall ISS database, graded by severity according to the TIMI criteria is provided in Table 6-2.

The distribution of bleeding events categorized by bleeding site, by indication and by treatment is shown in Table 6-3.

**Table 6-2**  
Bleeding Status of Bleeding Events Occurring at Any Time by Indication and Treatment Group

Bleeding Status	Coronary Angioplasty Studies				Unstable Angina Studies				All Studies			
	Integrelin (N=2736)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Major	125	4.6	61	4.5	3	1.5	0	0.0	128	4.4	61	4.2
Minor	351	12.8	119	8.8	18	8.9	6	5.6	369	12.6	125	8.6
Insignificant	1316	48.1	576	42.7	36	17.7	15	14.0	1352	46.0	591	40.6
None	852	31.1	537	39.8	146	71.9	86	80.4	998	34.0	623	42.8
Unresolved*	92	3.4	55	4.1	0	0.0	0	0.0	92	3.1	55	3.8

\* From 93-014: insufficient clinical information collected to allow CEC to classify

**Table 6-3**  
Bleeding Events Categorized by Bleeding Site by Indication and Treatment Group

Bleeding Site	Coronary Angioplasty				Unstable Angina				All Studies			
	Integrelin N = 2736		Placebo N = 1348		Integrelin N = 203		Placebo N = 107		Integrelin N = 2939		Placebo N = 1455	
	N	%	N	%	N	%	N	%	N	%	N	%
Patient with Major Bleeding Event	125	4.6	61	4.5	3	1.5	0	0.0	128	4.4	61	4.2
Femoral Artery Access site	89	3.3	37	2.7	0	0.0	0	0.0	89	3.0	37	2.5
Other Puncture Site	8	0.3	4	0.3	1	0.5	0	0.0	9	0.3	4	0.3
Retroperitoneal	5	0.2	3	0.2	0	0.0	0	0.0	5	0.2	3	0.2
Spontaneous Gross Hematuria	6	0.2	5	0.4	0	0.0	0	0.0	6	0.2	5	0.3
Other Genitourinary	8	0.3	3	0.2	0	0.0	0	0.0	8	0.3	3	0.2
Spontaneous Hematemesis	8	0.3	3	0.2	0	0.0	0	0.0	8	0.3	3	0.2
Other Gastrointestinal	15	0.5	7	0.5	1	0.5	0	0.0	16	0.5	7	0.5
Oral	7	0.3	1	0.1	0	0.0	0	0.0	7	0.2	1	0.1
Intracranial	4	0.1	1	0.1	0	0.0	0	0.0	4	0.1	1	0.1
Decrease in Hct/Hgb only	15	0.5	8	0.6	0	0.0	0	0.0	15	0.5	8	0.5
CABG related	34	1.2	23	1.7	0	0.0	0	0.0	34	1.2	23	1.6
Hemoptysis	4	0.1	5	0.4	0	0.0	0	0.0	4	0.1	5	0.3
Epistaxis	2	0.1	2	0.1	1	0.5	0	0.0	3	0.1	2	0.1
Echymoses/Petechiae	7	0.3	0	0.0	1	0.5	0	0.0	8	0.3	0	0.0
Other Sites	11	0.4	10	0.7	1	0.5	0	0.0	12	0.4	10	0.7
Patient with Minor Bleeding Events	351	12.8	119	8.8	18	8.9	6	5.6	369	12.6	125	8.6
Femoral Artery Access site	301	11.0	89	6.6	0	0.0	0	0.0	301	10.2	89	6.1
Other Puncture Site	14	0.5	3	0.2	3	1.5	1	0.9	17	0.6	4	0.3
Retroperitoneal	1	0.0	0	0.0	0	0.0	1	0.9	1	0.0	1	0.1
Spontaneous Gross Hematuria	55	2.0	14	1.0	6	3.0	0	0.0	61	2.1	14	1.0
Other Genitourinary	17	0.6	6	0.4	0	0.0	0	0.0	17	0.6	6	0.4
Spontaneous Hematemesis	27	1.0	14	1.0	1	0.5	1	0.9	28	1.0	15	1.0
Other Gastrointestinal	16	0.6	6	0.4	2	1.0	0	0.0	18	0.6	6	0.4
Oral	7	0.3	0	0.0	1	0.5	0	0.0	8	0.3	0	0.0
Decrease in Hct/Hgb only	19	0.7	6	0.4	1	0.5	0	0.0	20	0.7	6	0.4
CABG related	8	0.3	7	0.5	1	0.5	0	0.0	9	0.3	7	0.5
Hemoptysis	3	0.1	2	0.1	0	0.0	1	0.9	3	0.1	3	0.2
Epistaxis	8	0.3	3	0.2	0	0.0	0	0.0	8	0.3	3	0.2
Echymoses/Petechiae	11	0.4	0	0.0	2	1.0	1	0.9	13	0.4	1	0.1
Other Sites	7	0.3	3	0.2	1	0.5	0	0.0	8	0.3	3	0.2

**3.3.2 Investigator Reported Bleeding Events:** In all studies included in the ISS database, investigators rated bleeding complications (as well as other adverse events) as life threatening/severe, moderate, or mild.

The incidence of bleeding events rated as severe by the investigator is the same in the Integrilin- and placebo-treated groups (approximately 2.0%). The frequency of bleeding events rated as mild and moderate was higher in the Integrilin-treated group than in the placebo group.

There were fewer bleeding events reported in UA/NQMI patients than in patients undergoing coronary angioplasty.

The results of these ratings are shown in Table 6-4.

**Table 6-4**  
Investigator Ratings of Bleeding Event Severity Occurring at Any Time by Indication and Treatment Group\*

Investigator Rating of Severity of Bleeding Events	Coronary Angioplasty Studies				Unstable Angina Studies				All Studies			
	Integrilin (N=2736)		Placebo (N=1348)		Integrilin (N=203)		Placebo (N=107)		Integrilin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Severe	56	2.0	28	2.1	4	2.0	1	0.9	60	2.0	29	2.0
Moderate	289	10.6	97	7.2	6	3.0	3	2.8	295	10.0	100	6.9
Mild	1478	54.0	651	48.3	36	17.7	14	13.1	1514	51.5	665	45.7
Missing	2	0.1	1	0.1	2	1.0	1	0.9	4	0.1	2	0.1
Patients Without Bleeding Event	911	33.3	571	42.4	155	76.4	88	82.2	1066	36.3	659	45.3

\*Percentages based on total number of patients

**3.3.3 Intracranial Bleeding Events:** Four intracranial bleeding events were reported in patients treated with Integrilin and included in the ISS database. All four events occurred in patients undergoing coronary angioplasty. There was one intracranial bleeding event reported in a placebo-treated patient undergoing coronary angioplasty.

The incidence of intracranial bleeding in patients undergoing coronary angioplasty in the ISS database treated with Integrilin was 0.15% (4/2736) compared to 0.07% (1/1348) in placebo-treated patients.

No intracranial bleeding events were reported in the studies of patients with UA/NQMI. In addition, one intracranial bleeding event was reported in an Integrilin and Activase™ (alteplase) treated patient in the study of patients with acute myocardial infarction (IMPACT AMI, Study 92-011).