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			
F n=26	3.1	O/L	135	0.75			
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 ± 9.84. The post-coronary angioplasty percent stenosis was 21.7 ± 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 ± 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 and the IC 80

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 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
S.D.	0.78	0.53	1.05	1.08	0.28

At baseline, the overall mean bleeding time was 8 min. in all treatment groups. At 30 minutes 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 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	%
Bleeding Classification										
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
Number of Bleeding Events within 24 hr Post-Infusion										
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
Bleeding Severity										
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 (135/075 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 N (%)	Integrilin 90 µg/kg + 0.75 µg/kg-min N=5 N (%)	Integrilin 135 µg/kg + 0.5 µg/kg-min N=16 N (%)	Integrilin 135 µg/kg + 0.75 µg/kg-min N=27 N (%)	Integrilin 180 µg/kg + 1.0 µg/kg-min N=4 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[1]	1	2	3	4	6	12	16	24		30 Days	6 Mos.
Medical/Medication History	X										X	X	
Physical Examination	X									X	X	X	
Vital Signs[2]	X		X	X	X	X	X	X	X				
12 Lead ECG	X										X	X	
Hematology[3]	X										X	X	
PT/aPTT	X	← PRN to maintain heparin levels →									X		
Serum Chemistry[4]	X										X		
Urinalysis[5]	X										X		
Angiographic Assessment[6]	X	X											X
Anti-Integrelin Antibodies[7]	X											X	
Survey on Major Outcomes													X

1 EOP = immediately at the end of angioplasty procedure
2 Including heart rate, blood pressure, and temperature (temperature assessed less frequently than other vital signs). Vitals also assessed at infusion termination.
3 Including hemoglobin, hematocrit, total and differential leukocyte count
4 Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate
5 Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood
6 Follow-up tests performed in 600 patients at selected investigational sites
7 Testing performed only in the first 10 patients enrolled at each site
8 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	16	24	Prior to	Term	4	8	12	16	
Vital Signs[2] (see also above)									X					
Platelet Count	X	X	X		X				X					X
CK/CK-MB	X		X		X				X[9]					X
Mass Balance (plasma)[8]				X		X	X			X	X	X		
Mass Balance (urine)[8]				X		X	X				X		X	
Pharmacokinetics								X						

1 EOP = immediately at the end of angioplasty procedure
2 Including heart rate, blood pressure, and temperature (temperature assessed less frequently than other vital signs). Vitals also assessed at infusion termination
3 Including hemoglobin, hematocrit, total and differential leukocyte count
4 Including creatinine, BUN, alkaline phosphatase, SGOT, SGPT, glucose, sodium, potassium, chloride, bicarbonate
5 Including pH, specific gravity, protein/albumin, glucose, ketones, bilirubin, blood
6 Follow-up tests performed in 600 patients at selected investigational sites
7 Testing performed only in the first 10 patients enrolled at each site
8 Testing performed in 30 patients enrolled at Duke University Medical Center
9 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 α 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. audited key efficacy and safety variables for missing, out-of-range, or inconsistent values and identified the discrepant records

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 Integrilin and placebo-treated group was marginally significant ($p = 0.053$), mainly because of the increased incidence of unstable angina in the high dose Integrilin-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	792 (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%)	193 (14.9%)	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	59	60	59

* 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.

Nitrates were administered during the procedure to 91% of treated patients. No other single type of medication was administered to more than 8% of patients.

ANGIOPLASTY PARAMETERS AND ANGIOGRAPHY

The left anterior descending (LAD) artery was the most commonly affected (38%), followed by the right coronary artery (RCA) (33%), or the left circumflex (LCX) artery (23%). The distribution of culprit arteries appeared similar across groups.

The majority (70.0%) of patients underwent angioplasty for a single lesion; 98.3% of patients had three or fewer lesions treated. Most patients (99.2%) had a femoral approach. The majority (94.7%) of patients were treated with PTCA; the other most common treatments were DCA (11.6%) and Rotablator (9.8%). The angioplasty procedures were largely successful and, in general, similar rates of complications were observed among placebo- and Integrilin-treated patients. There was $\leq$ 50% stenosis in all lesions (angioplasty success) in 94.9% of high dose patients, 95.6% of low dose patients, and 94.2% of placebo patients.

EFFICACY RESULTS

The efficacy results are presented as follows:

1.0 Summary of the Composite Endpoint at 24 Hours, 30 Days, and 6 Months
2.0 Temporal Presentation of Composite Endpoint
  2.1 Abrupt Closure
  2.2 Composite Endpoint at 24 and 48 Hours and at 30 Days and Individual Components of the Composite Endpoint
  2.3 Six-Month Follow-Up Analyses and Individual Components
3.0 Composite Efficacy Endpoints and/or Any Interventions
4.0 Dose Response and the Composite Endpoint
5.0 Randomized vs. Treated Patient Analyses
6.0 The Composite Endpoint by Clinical Risk Strata
7.0 Investigators' Assessment of the Composite Efficacy Endpoint
8.0 Components of the Composite Endpoint
  8.1 Effect of Treatment on the First and on the Most Severe Endpoint
  8.2 Effect of Treatment on the Incidence of Subtypes of Mis
9.0 Effect of Investigational Site on the Composite Endpoint
10.0 Subgroup, Covariate and Multivariate Analyses
  10.1 Subgroups Analyses
  10.2 Multivariate Analyses

1.0 Summary of the Composite Endpoint at 24 hours, 30 days and 6 months:

The protocol-defined primary efficacy endpoint was a reduction in incidence of composite events of death, MI and urgent revascularization during the first 30 days after randomization.

The treated population was used as the primary analysis of efficacy because some patients were randomized before it was determined whether they met the all the enrollment criteria and before the final decision to proceed with angioplasty was made, therefore, some patients did not undergo angioplasty and did not receive study treatment. The randomized patient analysis was also performed to document consistency and exclude sources of bias occurred following randomization.

The incidences of the CEC adjudicated composite events and each individual component of the composite endpoint were determined at 24 and 48 hours after randomization and at 30 days and 6 months.

The administration of Integrilin produced a reduction in the composite endpoints compared to placebo. This frequency of the composite efficacy endpoints at 24 hours and at 30 days are summarized in table 7-1 and in Fig. 7-1.

Table 7-1: Incidence of CEC-Adjudicated Composite Events with Analysis at 24 hr and at 30 days.

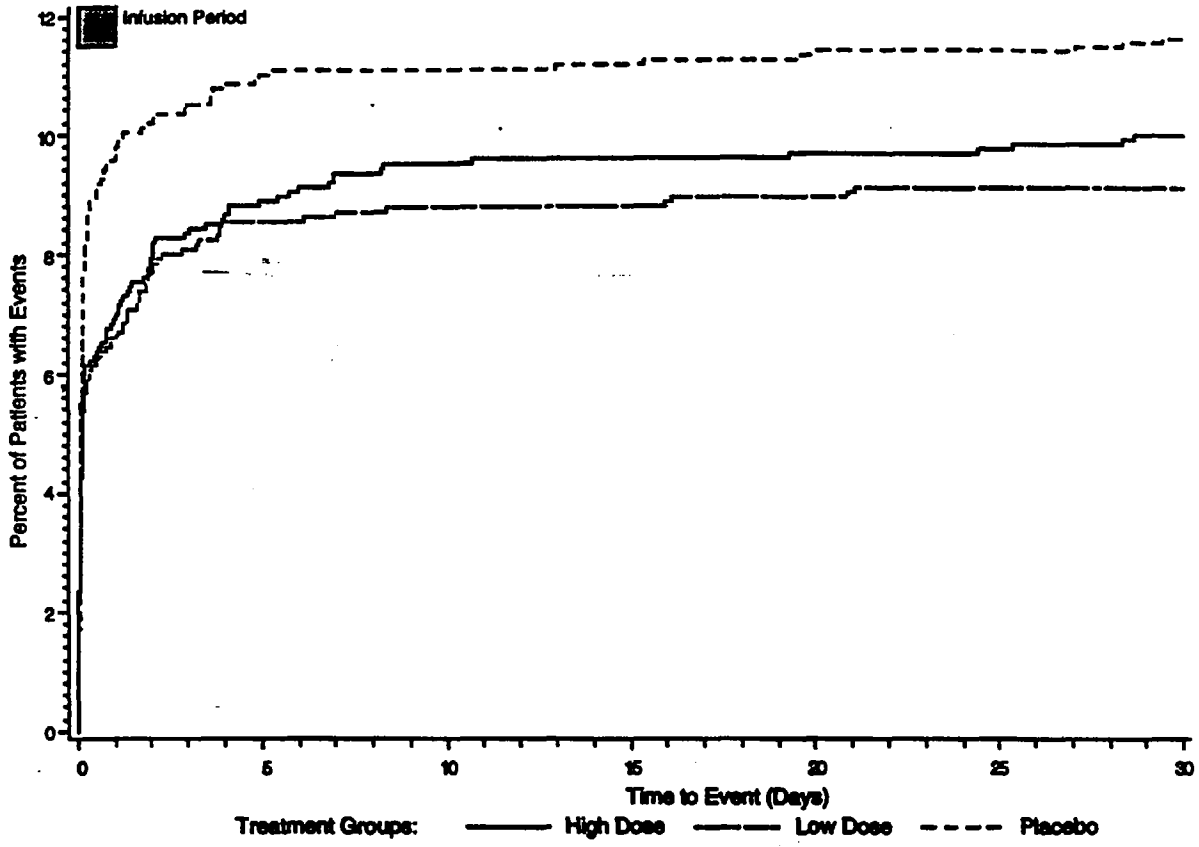
Time Point (composite end-points)	Integrilin High Dose (N = 1286)	Integrilin Low Dose (N = 1300)	Placebo (N = 1285)
24 hr (Death, MI, Urgent Intervention)	89 (6.9%)	86 (6.6%)	123 (9.6%)
% reduction* (P-Value)	28.1% (0.014)	31.3% (0.006)	--
30 D (Death, MI, Urgent Intervention)	128 (10.0%)	118 (9.1%)	149 (11.6%)
% reduction* (p-value)	13.8% (0.179)	21.6% (0.035)	--

A statistically significant reduction in composite endpoint was observed at 24 hours for both Integrilin regimens compared to placebo. At 30 days, the reduction remained statistically significant for the low dose Integrilin regimen. Similar statistical significance was observed using the log-rank and Wilcoxon tests ($p = 0.034$).

The majority of events (75%) which occur within the first 30 days post-randomization occurred very early (within 24 hours) in both Integrilin- and placebo-treated patients.

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



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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, Urgent 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, Urgent 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, Urgent 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, Any 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^2 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.

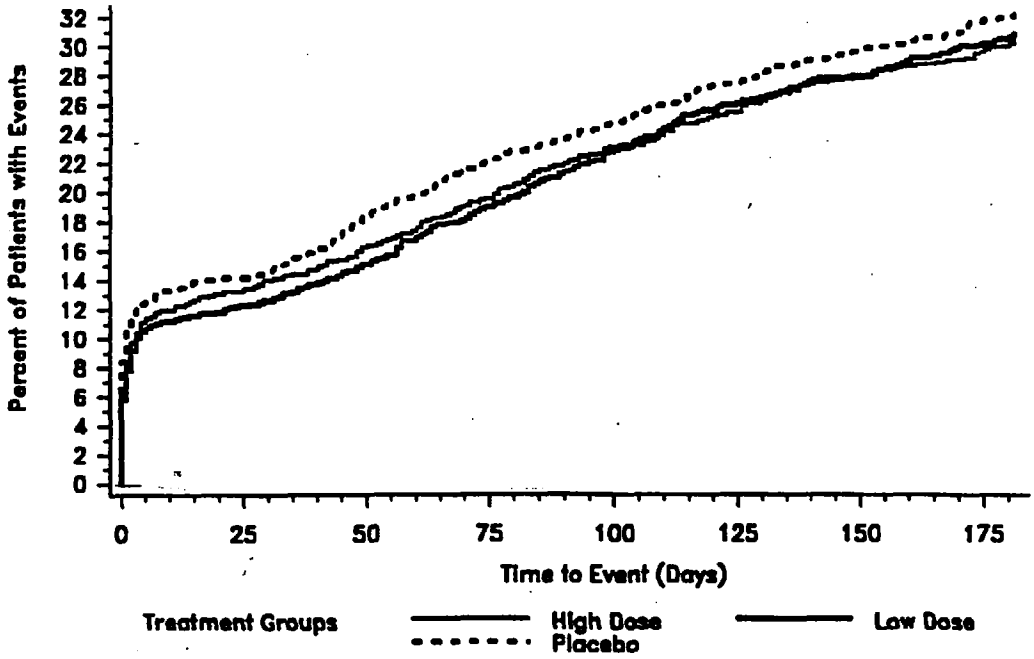

Figure 7-2: Frequency of Composite Endpoint (Death, MI, and/or Any Intervention) Over 6 Months for Treated Patients

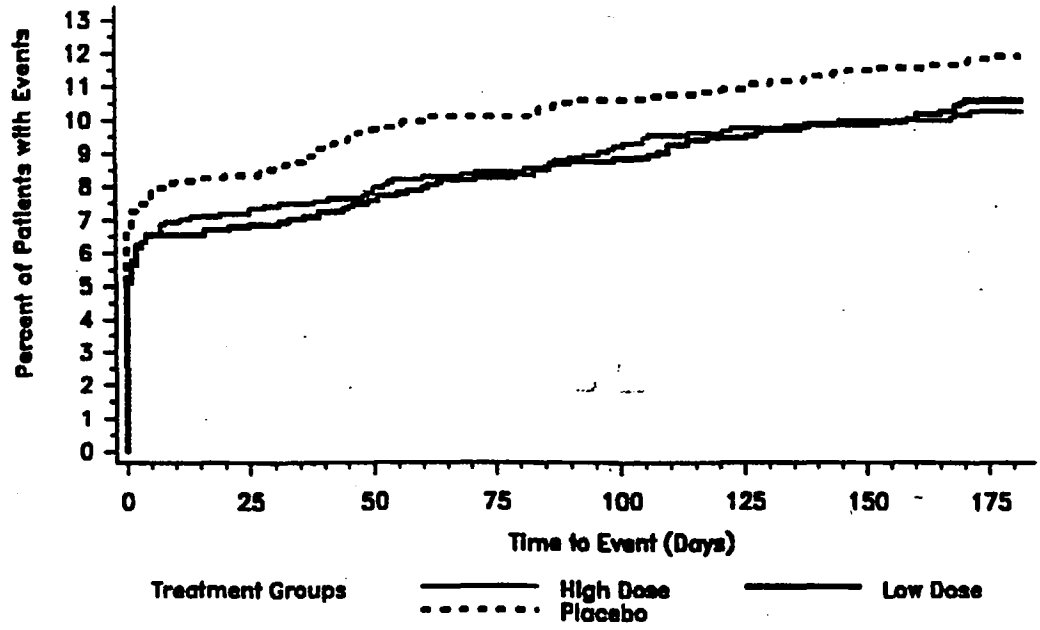

Figure 7-3: Frequency of Death and/or MI Over 6 Months for Treated Patients

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^2 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 Group s

Composite Endpoints	Integrilin High Dose (N=1286)	Integrilin LowDose (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^2 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

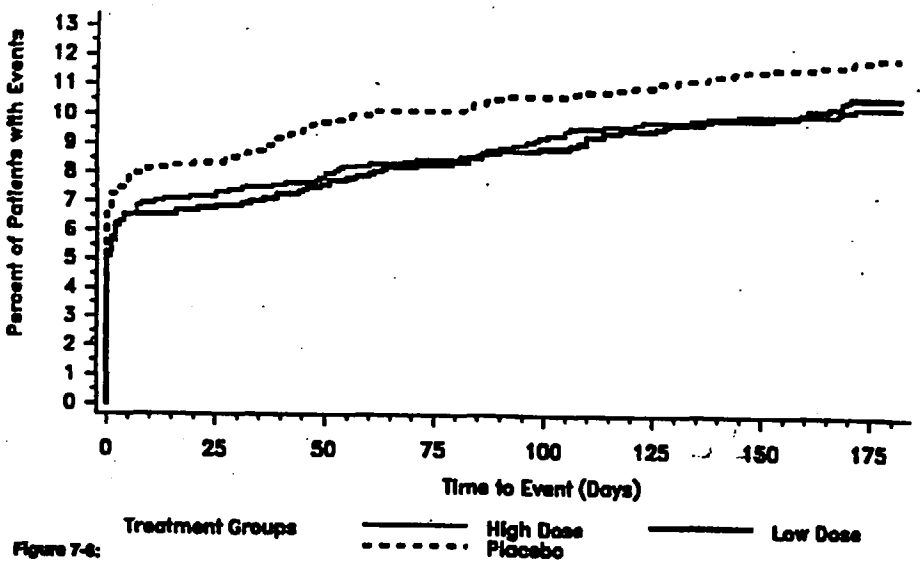

Figure 7-6:

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 Absolute Reduction	5.9% 1.9%	4.0% 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

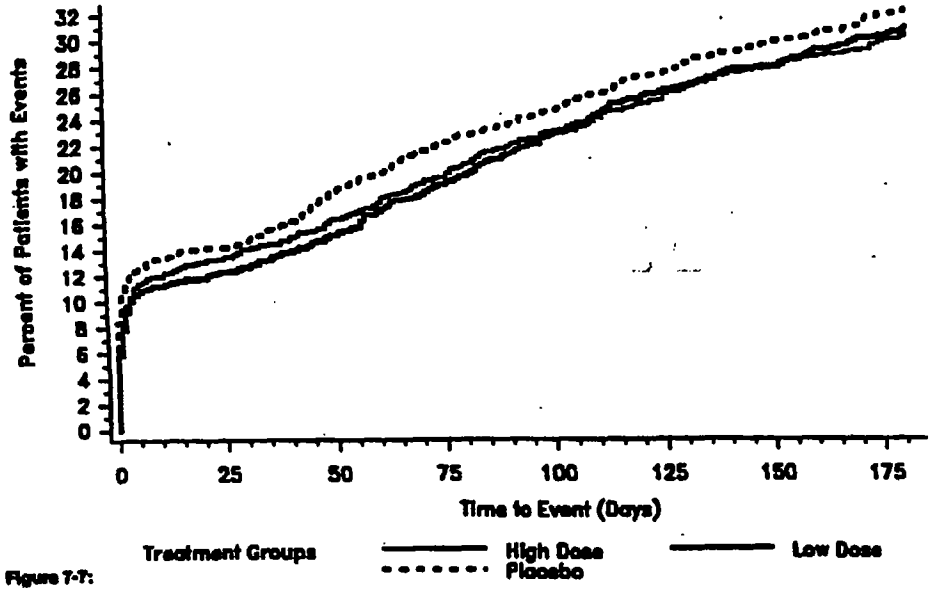

Figure 7-7:

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^2 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=1286)	Integrilin Low Dose (N=1300)	Placebo (N=1289)
24 Hours			
High Risk			
Composite Endpoint	96 (7.5%)	96 (7.5%)	46 (3.5%)
Death	1 (0.1%)	0	1 (0.1%)
Myocardial Infarction	69 (5.3%)	89 (6.9%)	84 (6.5%)
Urgent/Emergency Revascularization	6 (1.2%)	7 (1.4%)	11 (2.1%)
Emergency/Urgent CABG	5 (1.0%)	6 (1.2%)	10 (2.0%)
Stent Placement	2 (0.4%)	2 (0.4%)	5 (1.0%)
Elective			
Composite Endpoint	55 (6.7%)	60 (6.2%)	77 (6.7%)
Myocardial Infarction	40 (5.1%)	42 (5.2%)	88 (7.1%)
Urgent/Emergency Revascularization	7 (0.9%)	4 (0.5%)	11 (1.4%)
Emergency/Urgent CABG	6 (1.0%)	7 (0.9%)	18 (2.3%)
Stent Placement	5 (0.6%)	5 (0.6%)	12 (1.5%)
30 Days			
High Risk			
Composite Endpoint	51 (10.5%)	57 (11.6%)	57 (11.5%)
Death	8 (1.6%)	6 (1.2%)	7 (1.4%)
Myocardial Infarction	36 (7.5%)	38 (7.7%)	40 (8.1%)
Urgent/Emergency Revascularization	13 (2.6%)	24 (4.9%)	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%)
Elective			
Composite Endpoint	77 (8.7%)	61 (7.6%)	82 (11.6%)
Death	3 (0.4%)	6	7 (0.9%)
Myocardial Infarction	54 (6.8%)	46 (5.9%)	66 (8.4%)
Urgent/Emergency Revascularization	23 (2.5%)	11 (1.4%)	20 (2.5%)
Emergency/Urgent CABG	15 (1.5%)	8 (1.0%)	23 (2.9%)
Stent Placement	6 (0.6%)	5 (0.6%)	12 (1.5%)

[Source: Summary Tables E-02 and E-03; Summary Listing L-05]

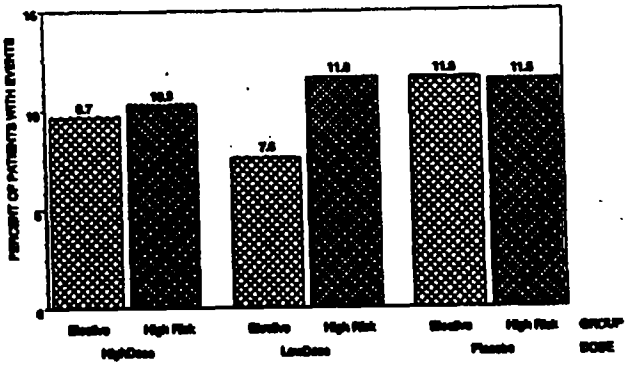

Figure 7-10: Incidence of CEC-Adjudicated Composite Endpoint at 30 Days f Treated Patients by Investigator Determined Risk Stratification (CRF) and Treatment Group

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

	Investigators' Assessment of Endpoints			CEC-Adjudicated Endpoints		
Post-Randomization Time Period	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)
24 hours*						
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)
Composite	**46 (3.6) †**	**45 (3.5) †**	**79 (6.1)**	**89 (6.9)+**	**86 (6.6)+**	**123 (9.6)**
48 hours*						
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)
Composite	**56 (4.4) †**	**54 (4.2) †**	**82 (6.4)**	**102 (7.9)**	**99(7.6)+**	**131 (10.2)**
30 Days*						
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)
Composite	**80 (6.2)**	**70 (5.4) †**	**97 (7.5)**	**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 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 summarizes in the following table.

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

	Most Severe Event and Composite Endpoints			First Event and Composite Endpoints		
Post-Randomization Time Period	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)
24 hours*						
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)
Composite	**89 (6.9)**	**86 (6.6)**	**123 (9.6)**	**89 (6.9)**	**86 (6.6)**	**123 (9.6)**
48 hours*						
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)
Composite	**102 (7.9)**	**99 (7.6)**	**131 (10.2)**	**102 (7.9)**	**99(7.6)**	**131 (10.2)**
30 Days*						
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)
Composite	**128 (10.0)**	**118 (9.1)**	**149 (11.6)**	**128 (10.0)**	**118 (9.1)***	**149 (11.6)**

*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

	Integrelin High Dose	Integrelin Low Dose	Placebo
At 24 Hours			
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%) 0.983	7 (0.5%)
Large Enzyme MI p* value vs. placebo	35 (2.7%) 0.031	39 (3.0%) 0.061	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%)
At 30 Days			
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%) 0.461	12 (0.9%) 0.333	17 (1.3%)
Large Enzyme MI p* value vs. placebo	53 (4.1%) 0.161	52 (4.0%) 0.118	68 (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%) 0.063	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 χ^2 Integrelin 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 invention 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.