SAFETY EVALUATIONS

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

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

BLEEDING ADVERSE EVENTS

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

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

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

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

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

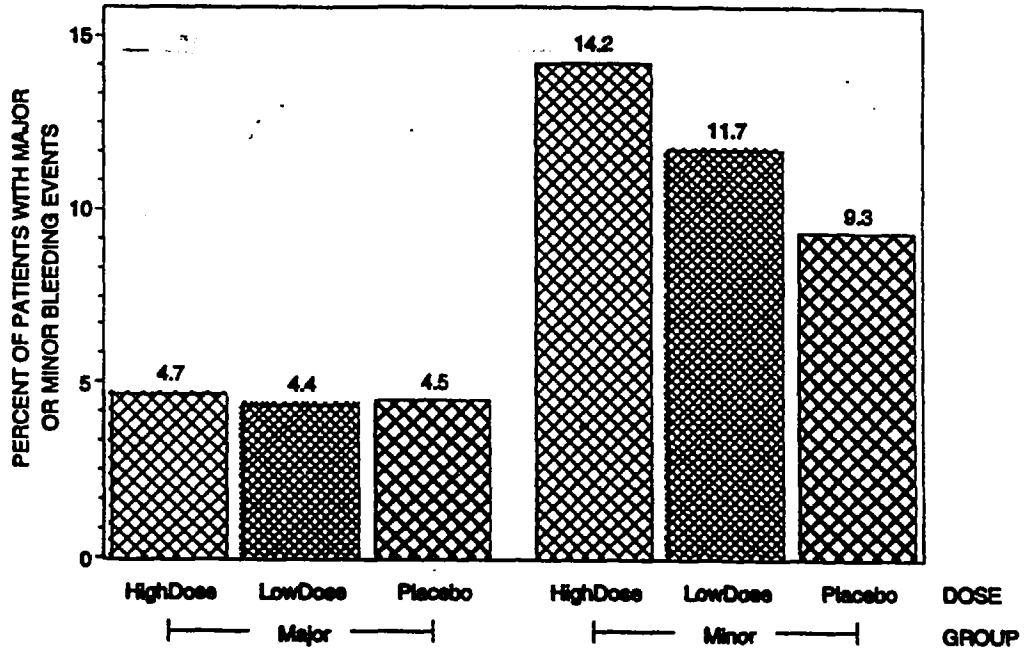
TIMI Bleeding	High Dose Integrilin	Low Dose Integrilin	Placebo
Total Patients*	1245	1249	1230
Major Bleeding	58 (4.7%)	55 (4.4%)	55 (4.5%)
Minor Bleeding	177 (14.2%)	146 (11.7%)	115 (9.3%)
Insignificant Bleeding	620 (49.8%)	650 (52.0%)	567 (46.1%)
No Bleeding	390 (31.3%)	398 (31.9%)	493 (40.1%)
Unresolved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

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

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

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

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



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

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

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

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

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

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

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

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

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

Bleeding Excluding Patients Undergoing Coronary Artery Bypass Graft (CABG) Surgery: The incidence of major bleeding was lower in the subgroup of non-surgical (non-CABG) patients compared to the overall population in this study. However, the incidence of major bleeding was higher in both Integrilin groups (2.7%) than in the placebo group (1.7%) in this population, although the number of patients was small.
The incidence of minor bleeding was only slightly less than the total population.
The most common site of bleeding (major and minor) was the femoral access site.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

NON-BLEEDING ADVERSE EVENTS

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

In subgroups defined by age, gender and ethnicity, treatment with Integrilin did not result in a clinically relevant increase in non-bleeding AEs compared with placebo. In the 18 patients with serum creatinine >2 mg/dL, (4 in the high dose, 7 in the low dose Integrilin and 7 in the placebo group) one intracranial bleeding with full recovery occurred in the high dose group.
Integrilin patients with major and minor bleeding had a higher incidence of hypotension and injection site reaction than patients without bleeding events.

Table 8-16

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

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

† Events with $p<0.05$ for likelihood ratio χ^2 tests of Integrelin vs. placebo

[Source: Summary Table S-47: Summary Listing L-601

Table 8-17

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

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

† Events with $p<0.05$ for χ^2 tests of integrelin vs. placebo.

[Source: Summary Table S-48; Summary Listing L-60]

DEATHS

The CEC determined the cause of death as cardiovascular (CV), non-CV, and of uncertain etiologies.
A total of 31 patients died within 30 days of randomization. The majority of deaths were from cardiac causes (table 8-22).

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

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

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

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

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

ADVERSE EVENTS LEADING TO STUDY DRUG DISCONTINUATION

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

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

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

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

+ A patient may have had more than one adverse event leading to study drug discontinuation
† $P < 0.05$ for X_2 test of Integrilin vs. placebo

SERIOUS ADVERSE EVENTS

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

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

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

Table 8-27

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

Bleeding Site or COSTART Preferred Term*	Integrilin High Dose (N=1286)	Integrilin Low Dose (N=1300)	Placebo (N=1285)
Any Serious Bleeding Event	78 (6.1%)	72 (5.5%)	52 (4.0%)
Bleeding Location			
Femoral Artery Access Site	55 (4.3%)	54 (4.2%)	34 (2.6%)
CABG Related	10 (0.8%)	9 (0.7%)	13 (1.0%)
Spontaneous Hematemesis	12 (0.9%)	4 (0.3%)	2 (0.2%)
Hct/Hgb Drop Only	4 (0.3%)	4 (0.3%)	5 (0.4%)
Other Sites	2 (0.2%)	6 (0.5%)	6 (0.5%)
Retroperitoneal	3 (0.2%)	4 (0.3%)	0
Spontaneous Gross Hematuria	2 (0.2%)	4 (0.3%)	2 (0.2%)
Oral	4 (0.3%)	2 (0.2%)	0
Other Puncture Site	3 (0.2%)	3 (0.2%)	0
Other Genitourinary	0	3 (0.2%)	1 (0.1%)
Other Gastrointestinal	2 (0.2%)	1 (0.1%)	3 (0.2%)
Intracranial	2 (0.2%)	1 (0.1%)	1 (0.1%)
Hemoptysis	3 (0.2%)	0	2 (0.2%)
Ecchymoses/Petechiae	2 (0.2%)	1 (0.1%)	0
Epistaxis	1 (0.1%)	0	0

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

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

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

Table 8-31

Incidence of Reasons for Rehospitalization Reported for 0.5% or More of Treated Patients in Any Treatment Group by Treatment Group

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

† $P < 0.05$ for χ^2 tests of Integrelin vs. placebo.

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

LABORATORY RESULTS

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

Hematologic Parameters: Decreases in Hgb/Hct between baseline and discharge were slightly greater for Integrilin than placebo patients and consistent with the higher rate of bleeding events in these groups. Mean Hgb levels were similar across treatment groups at baseline, discharge, and Day 30 and were within normal range at all time points. Within each treatment group, mean Hgb levels decreased from baseline to discharge (1.0 to 1.2 g/dL). By Day 30, mean Hgb levels had returned to near baseline levels in all groups.
Decreases in mean Hct paralleled the changes in Hgb in all groups. No clinically meaningful differences were observed among the treatment groups.

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

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

Mean platelet counts were similar across treatment groups at baseline and at subsequent time-points. Mean platelet counts remained within normal range at all evaluations. Decreases from mean baseline platelet counts were observed within all treatment groups at most post-baseline evaluations except 30 days. Analysis of changes from baseline to discharge and to Day 30 indicated no statistically significant differences between the treatment groups with respect to degree of change in platelet count. Mean nadir platelet counts were similar in all treatment groups. Less than 1% of patients had platelet counts $< 50{,}000/mm^3$.
In all treatment groups, more than 85% of patients had normal baseline counts that remained in the normal range. Percentages of patients with platelet counts decreased from normal baseline ranged with no large differences evident among the treatment groups.

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

Serum Chemistry

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

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

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

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

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

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

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

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

The proportion of patients that had a post-baseline CK >3 x ULN or >3 x baseline in the placebo group (6.5%) was statistically greater than the proportions of patients in the low dose (4.3%) or high dose (4.1%) Integrilin groups.
The smaller changes from baseline in CK observed in the Integrilin groups, as well as the significantly smaller percentage of Integrilin patients having CK >3 x ULN (defined in protocol as evidence of MI) compared to placebo are consistent with an effect of Integrilin on MI. This parameter was used by the CEC to ascertain MI occurrence per protocol.

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

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

CONCLUSIONS

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

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

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

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

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

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

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

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

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

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

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

Subgroup analyses also showed greater benefit from Integrilin in patients weighing

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

Integrilin was shown to be safe in both regimens studied. Bleeding events were the most common adverse events that appeared to be related to Integrilin therapy. Incidences of the most serious bleeding events, including major (according to the TIMI criteria) and severe bleeding (as assessed by the Principal Investigators), and the incidence of red blood cell transfusions were similar in both Integrilin treated groups and in the placebo group.
However, less clinically serious bleeding events, including minor, mild and moderate bleeding and study drug discontinuations due to bleeding were more common in Integrilin-treated patients, particularly in the high dose group. Furthermore, among the serious adverse events, bleeding events were more frequent in the integrilin groups than in the placebo groups, and study drug discontinuation because of bleeding occurred more frequently in the Integrilin groups than in the placebo group.

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

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

No laboratory abnormalities were associated with Integrilin therapy.
No effect of Integrilin of hepatic or renal function were noted. No increased incidence of thrombocytopenia was reported for the Integrilin groups compared to placebo.

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

No Integrilin antibodies were detected in 425 patients tested.

INTEGRATED SUMMARY OF EFFICACY (ISE)

Data Sets Analyzed:
- Studies in Coronary Angioplasty
- Studies in Unstable Angina

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

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

STUDIES IN CORONARY ANGIOPLASTY:

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

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

The IMPACT II clinical trial was a large, double-blind, multi-center study which examined the use of Integrilin in patients undergoing coronary angioplasty (balloon angioplasty, directional atherectomy, transluminal extraction catheter atherectomy, rotational ablation angioplasty or excimer laser angioplasty [PTCA]). The trial included 4010 patients and was carried out at 82 centers in the U.S..
A total of 139/4010 (3.5%) randomized patients, similarly distributed among the treatment groups, were not treated with study medication. This was due to the fact that many patients were enrolled before the final decision was made to proceed to angioplasty.

Two dosing regimens of Integrilin were each compared to placebo. The primary efficacy endpoint for the study was the composite occurrence of death, myocardial infarction and/or urgent coronary intervention.
Two methods of assessment of the composite endpoint, that of the Clinical Events Committee (CEC) and that of the Principal Investigators, were employed to investigate clinical efficacy and safety. The CEC was independent and blinded to study treatment. The CEC assessed all patients at all sites, thus eliminating individual investigator bias.

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

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

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

Pooled Efficacy Analysis (IMPACT I and IMPACT II): The results of the two studies are analyzed jointly because the initial IMPACT I and IMPACT II employed a similar endpoint - death, MI, and/or urgent intervention, both studies followed patients to 30 days and the component events were adjudicated under blinded conditions.
The regimens employed in the initial IMPACT and IMPACT II studies were different. IMPACT used a common bolus of 90 mg/kg and a continuous infusion of 1.0 mg/kg-min for either of two different durations (4 or 12 hours). IMPACT II used a common bolus of 135 mg/kg and two different rates of continuous infusion (0.50 or 0.75 mg/kg-min) for 20-24 hours.
Since there is no overlap of the regimens employed in the two studies, the pooled Integrilin patients were compared to the pooled placebo patients.

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

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

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

The majority of the clinical effect occurred during the period of administration, however, the absolute benefit accrued by patients receiving Integrilin remained after 30 days.
No withdrawal or rebound effect after cessation of therapy were observed.

STUDIES IN UNSTABLE ANGINA/NON Q-WAVE MYOCARDIAL INFARCTION

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

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

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

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

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

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

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

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

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

This study was an open-label study in which various dose regimens of Integrilin (120 mg/kg + 1.0 mg/kg-min, 135 mg/kg + 1.0 mg/kg-min, and 150 mg/kg + 1.25 mg/kg-min, either with or without heparin) were compared to heparin plus aspirin and a placebo Integrilin infusion (the control group) in patients with UA/NQMI. A total of 61 patients were randomized and 57 were treated including approximately 6 to 8 patients for each of the various Integrilin combinations and 18 patients in the control group. Infusions were to be continuous and last for 12 to 72 hours.
The sample sizes in this study preclude any meaningful comparison of treatment groups or a definitive dose-response analysis, however, symptomatic ischemia was reported in 33% (6/18) of patients in the control group and in 23% (9/39) of patients who received Integrilin.

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

INTEGRATED SUMMARY OF SAFETY (ISS)

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

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

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

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

The ISS database in the NDA is derived from the three studies of Integrilin as adjunctive therapy to coronary angioplasty (PTCA) and from the three studies in Unstable Angina/Non Q-Wave Myocardial Infarction (UA/NQMI) since patients with UA/NQMI represent a subset of patients undergoing PTCA.
These six studies are integrated into one pooled database and tabulations are presented on the entire ISS database. Because of demographic and dose differences between the two patient populations (i.e., the coronary angioplasty patient population and the UA/NQMI patient population) separate analyses and comparisons within the ISS database are performed when appropriate.
A total of 4394 patients in the ISS database actually received treatment with either Integrilin (2939) or a matching placebo (1455). At least 88% of the ISS database is represented by the IMPACT II study.
Data from studies not included in the ISS database (Clinical Pharmacology studies) are discussed separately.

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

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

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

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

* One study with two separate patient populations.
** Database not finalized by November 30, 1995

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

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

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

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

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

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

RESULTS OF ISS

The sections addressed in this ISS are as follows:

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

1.0 Demographics

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

The 319 patients from the three studies in UA/NQMI represented only 7% of the ISS database, however, the demographics of the patients enrolled in the studies of Integrilin in the treatment of UA/NQMI were different from the patients enrolled in the coronary angioplasty studies. In general, the patients with unstable angina were older and there were higher proportions of black and female patients than in the studies in coronary angioplasty.
The demographic data by indication and by treatment are summarized in table 4-1

Table 4-1
Demographics by Indication and Treatment Group

Demographic Characteristic	Coronary Angioplasty Studies			Unstable Angina Studies			Total		
	Integrelin	Placebo	Total	Integrelin	Placebo	Total	Integrelin	Placebo	Total
Gender									
Male	2045 (74.7%)	1018 (75.5%)	3063 (75.0%)	118 (58.1%)	69 (64.5%)	187 (60.3%)	2163 (73.6%)	1087 (74.7%)	3250 (74.0%)
Female	691 (25.3%)	330 (24.5%)	1021 (25.0%)	85 (41.9%)	38 (35.5%)	123 (39.7%)	776 (26.4%)	368 (25.3%)	1144 (26.0%)
Total	2736	1348	4084	203	107	310	2939	1455	4394
Ethnicity									
Caucasian	2516 (92.1%)	1217 (90.4%)	3733 (91.6%)	31 (79.5%)	11 (61.1%)	42 (73.7%)	2547 (91.9%)	1228 (90.0%)	3775 (91.3%)
Black	111 (4.1%)	75 (5.6%)	186 (4.6%)	7 (17.9%)	5 (27.8%)	12 (21.1%)	118 (4.3%)	80 (5.9%)	198 (4.8%)
Asian	6 (0.2%)	4 (0.3%)	10 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (0.2%)	4 (0.3%)	10 (0.2%)
Hispanic	69 (2.5%)	41 (3.0%)	110 (2.7%)	1 (2.6%)	2 (11.1%)	3 (5.3%)	70 (2.5%)	43 (3.2%)	113 (2.7%)
Other	29 (1.1%)	9 (0.7%)	38 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (1.0%)	9 (0.7%)	38 (0.9%)
Total	2731	1346	4077	164	89	253	2770	1364	4134
Missing	5	2	7	39	18	57	169	91	260
Age									
20-29	2 (0.1%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	1 (0.1%)	3 (0.1%)
30-39	84 (3.1%)	30 (2.2%)	114 (2.8%)	5 (2.5%)	6 (5.6%)	11 (3.5%)	89 (3.0%)	36 (2.5%)	125 (2.8%)
40-49	426 (15.6%)	225 (16.7%)	651 (15.9%)	20 (9.9%)	11 (10.3%)	31 (10.0%)	446 (15.2%)	236 (16.2%)	682 (15.5%)
50-59	801 (29.3%)	416 (30.9%)	1217 (29.8%)	53 (26.1%)	24 (22.4%)	77 (24.8%)	854 (29.1%)	440 (30.2%)	1294 (29.4%)
60-69	859 (31.4%)	409 (30.3%)	1268 (31.0%)	63 (31.0%)	38 (35.5%)	101 (32.6%)	922 (31.4%)	447 (30.7%)	1369 (31.2%)
≥70	564 (20.6%)	267 (19.8%)	831 (20.3%)	62 (30.5%)	28 (26.2%)	90 (29.0%)	626 (21.3%)	295 (20.3%)	921 (21.0%)
Total	2736	1348	4084	203	107	310	2939	1455	4394
Age									
N	2736	1348	4084	203	107	310	2939	1455	4394
Mean	59.7	59.6	59.7	62.4	61.4	62.1	59.9	59.7	59.8
SD	10.76	10.75	10.76	10.37	10.97	10.58	10.75	10.77	10.76

Table 4-1 (Cont)

Demographics by Indication and Treatment Group

Demographic Characteristic	Coronary Angioplasty Studies			Unstable Angina Studies			Total		
	Integrelin	Placebo	Total	Integrelin	Placebo	Total	Integrelin	Placebo	Total
Hypertension									
No	1245 (45.6%)	611 (45.4%)	1856 (45.5%)	73 (36.0%)	43 (40.2%)	116 (37.4%)	1318 (44.9%)	654 (45.0%)	1972 (44.9%)
Yes	1487 (54.4%)	735 (54.6%)	2222 (54.5%)	130 (64.0%)	64 (59.8%)	194 (62.6%)	1617 (55.1%)	799 (55.0%)	2416 (55.1%)
Total	2732	1346	4078	203	107	310	2935	1453	4388
Missing	4	2	6				4	2	6
Diabetes									
No	2109 (77.1%)	1042 (77.5%)	3151 (77.2%)	147 (72.4%)	75 (70.1%)	222 (71.6%)	2256 (76.8%)	1117 (76.9%)	3373 (76.9%)
Yes	625 (22.9%)	303 (22.5%)	928 (22.8%)	56 (27.6%)	32 (29.9%)	88 (28.4%)	681 (23.2%)	335 (23.1%)	1016 (23.1%)
Total	2734	1345	4079	203	107	310	2937	1452	4389
Missing	2	3	5				2	3	5
Cerebral Vascular Disease									
No	2682 (98.1%)	1318 (98.0%)	4000 (98.1%)	191 (94.1%)	100 (93.5%)	291 (93.9%)	2873 (97.9%)	1418 (97.7%)	4291 (97.8%)
Yes	51 (1.9%)	27 (2.0%)	78 (1.9%)	12 (5.9%)	7 (6.5%)	19 (6.1%)	63 (2.1%)	34 (2.3%)	97 (2.2%)
Total	2733	1345	4078	203	107	310	2936	1452	4388
Missing	3	3	6				3	3	6
Peripheral Vascular Disease									
No	2558 (93.6%)	1257 (93.7%)	3815 (93.6%)	185 (91.1%)	99 (92.5%)	284 (91.6%)	2743 (93.5%)	1356 (93.6%)	4099 (93.5%)
Yes	174 (6.4%)	85 (6.3%)	259 (6.4%)	18 (8.9%)	8 (7.5%)	26 (8.4%)	192 (6.5%)	93 (6.4%)	285 (6.5%)
Total	2732	1342	4074	203	107	310	2935	1449	4384
Missing	4	6	10				4	6	10

2.0 Extent of Exposure

Dosing information was not available on 66 of the 2939 patients treated with Integrilin. The majority of the patients (64/66) without Integrilin dosing information were enrolled in IMPACT II study. The remaining two patients without dosing information were in IMPACT I study.
The extent of exposure to study treatments was characterized in two ways: cumulative dose (divided into $\leq$700, 700-850, 850-1000, 1000-1150, and $\geq$1150 ug/kg) and duration of exposure (divided into $\leq$ 12, 12-24, 24-48, and $\geq$48 hours).

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

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

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

2.2 Duration of Exposure: Depending on the study and the indication, the protocol defined duration of Integrilin infusion varied from 4 hours up to 72 hours.
For studies of patients undergoing coronary angioplasty, the majority of the patients were exposed to Integrilin for a period of time consistent with that expected dosage recommendations in the proposal package insert (i.e., 20-24 hours).
The majority of patients in the ISS database (77%) received an Integrilin infusion lasting between 12 and 24 hours. Approximately 13% of patients in the ISS database treated with Integrilin have received infusions lasting longer than 24 hours. Another 10% of patients treated with Integrilin have received infusion lasting less than 12 hours.
The patients who received an infusion of Integrilin for greater than 48 hours (n=48) were all in the UA/NQMI studies. In this group, 48% were females compared with approximately 26% of females in the overall ISS database, and 48% was over the age of 70 compared to 21% in the overall population.

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

Table 5-1
Total Cumulative Dose by Study*

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

*Patients with Integrelin dose information only

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

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

*Patients with Integrelin dose information only

3.0 Adverse Events

3.1 Adverse Events in ISS Database: Overall, there was twice the frequency of adverse event reporting in the patients undergoing coronary angioplasty than in patients with UA/NQMI. This was related to three factors:
1).The inclusion of adverse events potentially attributable to the angioplasty procedure, such as the insertion of arterial catheters and the effects of the use of angioplasty devices;
2).The difference in data collection methods (primarily spontaneous reporting versus elicited adverse events in the large IMPACT II study); and
3).The duration of observation (30 days in coronary angioplasty versus 24 hours post-treatment/hospital discharge in UA/NQMI studies).

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

3.2 Safety Results in Healthy Volunteer Subjects Not in the ISS Database : Adverse events reported in the five Phase I studies in healthy human volunteers were rare. The overall incidence of any event was 64.2% in the Integrilin group compared to 70% in the placebo group. No severe or life-threatening events were reported. The most common adverse event in volunteers receiving Integrilin was bleeding at an injection site.

There were no clinically significant trends in laboratory test results.

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

3.3.1 Bleeding According to TIMI Criteria: The overall incidence of major bleeding events was low and was similar in the Integrilin group and the placebo group. Patients undergoing angioplasty had a higher rate of major bleeding events due to the invasive procedure than did patients with UA/NQMI.
Overall the incidence rates of minor and insignificant bleeding events were higher among Integrilin-treated patients compared to placebo-treated patients, mainly in patients undergoing PTCA compared to the patients with UA/NQMI.
The most common site of major bleeding was the femoral artery access site and CABG related bleeding. The distribution of sites of bleeding events was similar between treatment groups.

The incidence of bleeding in the overall ISS database, graded by severity according to the TIMI criteria is provided in Table 6-2.
The distribution of bleeding events categorized by bleeding site, by indication and by treatment is shown in Table 6-3.

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

Bleeding Status	Coronary Angioplasty Studies				Unstable Angina Studies				All Studies			
	Integrelin (N=2736)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Major	125	4.6	61	4.5	3	1.5	0	0.0	128	4.4	61	4.2
Minor	351	12.8	119	8.8	18	8.9	6	5.6	369	12.6	125	8.6
Insignificant	1316	48.1	576	42.7	36	17.7	15	14.0	1352	46.0	591	40.6
None	852	31.1	537	39.8	146	71.9	86	80.4	998	34.0	823	42.6
Unresolved*	92	3.4	55	4.1	0	0.0	0	0.0	92	3.1	55	3.8

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

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

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

3.3.2 Investigator Reported Bleeding Events: In all studies included in the ISS database, investigators rated bleeding complications (as well as other adverse events) as life threatening/severe, moderate, or mild.
The incidence of bleeding events rated as severe by the investigator is the same in the Integrilin- and placebo-treated groups (approximately 2.0%). The frequency of bleeding events rated as mild and moderate was higher in the Integrilin-treated group than in the placebo group.
There were fewer bleeding events reported in UA/NQMI patients than in patients undergoing coronary angioplasty.

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

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

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

*Percentages based on total number of patients

3.3.3 Intracranial Bleeding Events: Four intracranial bleeding events were reported in patients treated with Integrilin and included in the ISS database. All four events occurred in patients undergoing coronary angioplasty. There was one intracranial bleeding event reported in a placebo-treated patient undergoing coronary angioplasty.
The incidence of intracranial bleeding in patients undergoing coronary angioplasty in the ISS database treated with Integrilin was 0.15% (4/2736) compared to 0.07% (1/1348) in placebo-treated patients.
No intracranial bleeding events were reported in the studies of patients with UA/NQMI. In addition, one intracranial bleeding event was reported in an Integrilin and Activase™ (alteplase) treated patient in the study of patients with acute myocardial infarction (IMPACT AMI, Study 92-011).

3.4 Non-Bleeding Adverse Events in the ISS Database: Common adverse events were defined as occurring at a frequency of greater than or equal to 2.0% in either the Integrilin-treated group or the placebo group. Adverse events that were reported at a frequency of less than 2% were reviewed to identify unusual but potentially serious adverse events (e.g., intracranial bleeding events). Because MI was evaluated as a clinical endpoint, it is not included as a common adverse event. The most frequently reported non-bleeding adverse events were those potentially related to an angioplasty procedure or the underlying disease. These events were reported at similar rates in both the Integrilin- and the placebo-treated patients. Hypotension and discomfort at the vascular access site were significantly more common in patients receiving Integrilin and were likely due to bleeding rather than to a an independent effect of Integrilin therapy.

To determine any possible relationships among the three most commonly reported adverse events and the incidence of bleeding associated with treatment with Integrilin in the IMPACT II study, the distribution of bleeding status was analyzed by the presence of hypotension, back pain, and injection site reaction.
The incidences of hypotension and, to a lesser extent, injection-site reaction increased with increasing severity of CEC-adjudicated bleeding in all three treatment groups suggesting that these two adverse events may be related, at least in part, to the bleeding.

The frequency of non-bleeding adverse events in patients with UA/NQMI was less than half of the frequency of adverse events in the overall ISS database. A total of 71 adverse events were reported in the Integrilin-treated patients (35.0%) and 35 (32.7%) events were reported in the placebo patients. Although they occurred at a lower frequency, the distribution of non-bleeding adverse events in the UA/NQMI studies were similar to those in the overall ISS database.
Back pain was less frequent in the Integrilin-treated or placebo-patients with UA/NQMI as patients with UA/NQMI were confined to bed rest less often than patients undergoing coronary angioplasty. Reflecting the lower incidence of bleeding events in patients with UA/NQMI, hypotension was uncommon, with only two patients (Integrilin-treated) having this adverse event.

Non-bleeding adverse events unrelated to underlying cardiac disease occurring more often in Integrilin patients than placebo patients were back pain (5.4% vs 1.9%), headache (13.8% vs 6.4%), nausea/vomiting (3.9% vs 0.0%). Higher cumulative doses and longer durations of treatment were used in the patients with UA/NQMI.

The common adverse events are summarized in Table 6-11.

Table 6-11

Frequency Of Most Common Non-Bleeding Adverse Events (>2%) Occurring at Any Time

Body System / Adverse Event	Coronary Angioplasty Studies				Unstable Angina Studies				Total			
	Integrelin N=2736		Placebo N=1348		Integrelin N=203		Placebo N=107		Integrelin N=2939		Placebo N=1455	
	N	%	N	%	N	%	N	%	N	%	N	%
ANY NON BLEEDING ADVERSE EVENT	2315	84.6	1100	81.6	71	35.0	35	32.7	2386	81.2	1135	78.0
ANY CARDIOVASCULAR EVENTS	1311	47.9	622	46.1	27	13.3	17	15.9	1338	45.5	639	43.9
Chest Pain/Angina	755	27.6	378	28.0	12	5.9	9	8.4	767	26.1	387	26.6
Hypotension	575	21.0	228	16.9	2	1.0	0	0.0	577	19.6	228	15.7
Bradycardia	143	5.2	69	5.1	1	0.5	0	0.0	144	4.9	69	4.7
Atrial Fibrillation	62	2.3	41	3.0	1	0.5	0	0.0	63	2.1	41	2.8
Hypertension	59	2.2	29	2.2	0	0.0	0	0.0	59	2.0	29	2.0
ANY DIGESTIVE	745	27.2	360	26.7	14	6.9	4	3.7	759	25.8	364	25.0
Nausea/Vomiting	653	23.9	317	23.5	8	3.9	0	0.0	661	22.5	317	21.8
Dyspepsia	65	2.4	31	2.3	2	1.0	3	2.8	67	2.3	34	2.3
ANY NERVOUS	347	12.7	157	11.6	12	5.9	5	4.7	359	12.2	162	11.1
Anxiety	83	3.0	47	3.0	2	1.0	0	0.0	85	2.9	41	2.8
Nervous/Agitated	81	3.0	32	2.4	0	0.0	0	0.0	81	2.8	32	2.2
Abnormal Thinking	56	2.0	35	2.6	4	2.0	4	3.7	60	2.0	39	2.7
ANY GENERAL BODY	1820	66.5	868	64.4	40	19.7	15	14.0	1860	63.3	883	60.7
Back Pain	1392	50.9	643	47.7	11	5.4	2	1.9	1403	47.7	645	44.3
Headache	411	15.0	215	15.9	28	13.8	9	8.4	439	14.9	224	15.4
Fever/Chills	279	10.2	145	10.8	1	0.5	2	1.9	280	9.5	147	10.1
Pain	244	8.9	119	8.8	3	1.5	0	0.0	247	8.4	119	8.2
Discomfort at Injection Site	252	9.2	99	7.3	0	0.0	0	0.0	252	8.6	99	6.8
Abdominal Pain	89	3.3	57	4.2	4	2.0	0	0.0	93	3.2	57	3.9

3.5 Deaths: The most frequent causes of death were related to the underlying cardiovascular disease. The clinical studies included in the ISS database showed an overall incidence of death at 30 days from enrollment of 0.9% (39/4394) which included an incidence of 0.8% (23/2939) in Integrilin-treated patients and 1.1% (16/1455) in placebo-treated patients (table 6-13). There was a total of 43 deaths reported after 30 days from enrollment. Two of these deaths were reported as 6-month clinical endpoints in the IMPACT I study with no information on cause of death, the remaining 41 deaths occurred after 30 days during 6 month follow-up of IMPACT II study (table 6-16).

Table 6-13

Cause of Death to 30 Days from Enrollment by Indication and Treatment Group

COSTART Code	Coronary Angioplasty		Unstable Angina Studies		All Studies		
	Integrelin (N=2736)	Placebo (N=1348)	Integrelin (N=203)	Placebo (N=107)	Integrelin (N=2939)	Placebo (N=1455)	Total (N=4394)
Any Death	18	15	5	1	23	16	39
Myocardial Infarction	7	7	0	0	7	7	14
Intracranial Bleed	3	0	0	0	3	0	3
Right Heart Failure	1	0	0	0	1	0	1
Heart Arrest	0	0	1	0	1	0	1
Sudden Death	2	2	0	0	2	2	4
Ventricular Fibrillation	0	0	1	0	1	0	1
Peripheral Vascular Disease	0	0	1	0	1	0	1
Shock	0	1	0	1	0	2	2
Other	5	5	2	0	7	5	12

Table 6-16

Patient Deaths from 30 Days Through 6 Months in the IMPACT II Study

CEC Information	Treatment Group		
	High Dose (N=1286)	Low Dose (N=1300)	Placebo (N-1285)
Cause of Death	N=10	N=17	N=14
Sudden Death	3	7	2
MI	1	4	4
Noncardiac medical/procedural	1	2	2
CHF	3	0	1
Other	2	4	5

Table 6-14 describes the patient deaths that occurred up to 30 days from enrollment.

Table 6-14
Patient Deaths to 30 Days from Enrollment in the ISS Database

Treatment Group	Patient ID	Gender/Age/ Weight	Study Drug Infusion Duration	Time from Enrollment to Death	Cause of Death
Integrelin	91-007B-10017	Male/57/87.2	48.4	2	Ventricular Fibrillation
	91-007B-12008	Male/74/85.4	72.0	-	-
	92-009-04009	Male/71/79.1	5.0	6	Intracranial Hemorrhage
	92-010A-25003	Male/65/68.0	17.8	4	During or post cardiac surgery
	93-014-14011	Female/77/95.0	24.7	14	Sudden Death
	93-014-19049	Male/66/93.0	0.7	2	Definite MI
	93-014-23039	Male/61/77.0	15.6	2	Intracranial Hemorrhage
	93-014-34072	Male/77/85.0	10.1	8	Other (Lobar Pneumonia ARDS)
	93-014-44016	Male/63/77.0	8.5	1	Definite MI
	93-014-48029	Male/62/75.0	24.1	2	Noncardiac (Respiratory Failure)
	93-014-49050	Female/71/56.0	0.7	2	Definite MI
	93-014-54012	Male/75/119.0	24.1	2	Intracranial Hemorrhage
	93-014-61034	Female/72/105.0	21.2	3	Definite MI
	93-014-62001	Female/60/87.8	23.6	16	Sudden Death
	93-014-63004	Male/68/96.0	24.0	4	Congestive Heart Failure
	93-014-64031	Female/72/97.0	11.4	1	Definite MI
	93-014-66061	Male/60/77.5	21.8	7	Other (Rupture AAA)
	93-014-91007	Male/67/68.0	0.8	0	During or post cardiac surgery
	93-014-94009	Male/59/74.0	22.9	30	Definite MI
	93-014-94021	Male/45/95.0	24.3	4	Unknown
	93-014-97004	Female/63/77.0	9.5	11	Possible MI
	93-015-56504	Female/63/43.8	19.4	2	Peripheral Vascular Disease
	93-015-62537	Male/69/83.1	12.6	12	VF Arrest
Placebo	92-009-05015	Male/79/88.0	1.3	0	Shock
	93-014-27007	Male/53/101.0	18.8	1	During or post cardiac surgery
	93-014-27060	Male/57/81.3	23.8	5	Noncardiac (Respiratory Coagulopathy, DIC)
	93-014-33015	Female/63/44.0	1.3	2	Noncardiac medical/procedural
	93-014-49045	Female/59/72.0	0.4	1	Definite MI
	93-014-55044	Female/71/77.1	19.2	2	Definite MI
	93-014-58016	Male/69/103.6	16.0	26	Noncardiac (Aspiration pneumonia)
	93-014-62008	Male/68/88.9	20.2	3	Definite MI
	93-014-62049	Male/69/87.8	20.3	6	Sudden Death
	93-014-67031	Female/62/70.8	19.8	8	Definite MI
	93-014-73024	Male/71/86.0	14.2	9	Noncardiac (Extensive thrombus)
	93-014-76012	Male/70/84.8	1.3	7	Definite MI
	93-014-84057	Female/66/80.0	23.6	1	Definite MI
	93-014-86032	Male/60/72.6	24.1	30	Sudden Death
	93-014-94034	Male/67/81.0	23.7	7	Definite MI
	93-015-47502	Male/74/88.2	18.0	29	Shock

3.6 Discontinuation due to Adverse Events: The proportion of patients discontinuing study drug because of an adverse event was higher in the Integrilin-treated group (5.4%) than in placebo group (3.5%).

Study drug discontinuation was primarily due to bleeding and cardiovascular events (similar in Integrilin-and placebo-treated patients). The most common bleeding site was the femoral artery access site. As a result, Integrilin-treated patients were more likely than placebo patients to discontinue study drug because of bleeding events at the femoral artery access site.

Table 6-17 summarizes the patients who discontinued treatment due to adverse events.

Table 6-17
Discontinuations Due to Adverse Events by Body System and Indication

Body System/ COSTART Term	Coronary Angioplasty		Unstable Angina		Total	
	Integrelin (N=2736)	Placebo (N=1348)	Integrelin (N=203)	Placebo (N=107)	Integrelin (N=2939)	Placebo (N=1455)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any AE	148 (5.4)	43 (3.2)	10 (4.9)	8 (7.5)	158 (5.4)	51 (3.5)
Bleeding	111 (4.1)	26 (1.9)	6 (3.0)	0	117 (4.0)	26 (1.8)
Femoral Artery Access Site	85 (3.1)	14 (1.0)	0	0	85 (2.9)	14 (1.0)
Hematemesis	11 (0.4)	4 (0.3)	1 (0.5)	0	12 (0.4)	4 (0.3)
Hematuria	10 (0.4)	0	1 (0.5)	0	11 (0.4)	0
Other Bleeding	31 (1.1)	10 (0.8)	6 (3.0)	0	37 (1.2)	10 (0.8)
Whole Body	9 (0.3)	1 (0.1)	1 (0.5)	0	10 (0.3)	1 (0.1)
Cardiovascular	38 (1.4)	19 (1.4)	2 (1.0)	7 (6.5)	40 (1.4)	26 (1.8)
Digestive	9 (0.3)	0	0	0	9 (0.3)	0
Thrombocytopenia	7 (0.3)	0	0	0	7 (0.2)	0
Nervous	10 (0.4)	3 (0.2)	1 (0.5)	1 (0.9)	11 (0.4)	4 (0.3)
Respiratory	3 (0.1)	1 (0.1)	0	0	3 (0.1)	1 (0.1)
Other	3 (0.1)	0	0	0	3 (0.1)	0

3.7 Serious Adverse Events: Adverse events were reviewed to identify patients who experienced potentially serious adverse events. Events reviewed included those events identified as severe by the investigator; those that resulted in premature discontinuation of study drug, rehospitalization, or an acute medical intervention; and those unresolved at discharge. Patients with major bleeding events were also identified as having serious adverse events. In addition, laboratory data were reviewed for extreme values for platelets, creatinine, and SGPT.

In general, serious adverse events were related either to bleeding or ischemic events. Patients receiving Integrilin had a higher incidence of serious bleeding events in patients undergoing coronary angioplasty (7.2% versus 6.3%) as well as in patients with UA/NQMI (4.4% versus 0.9%). In patients undergoing coronary angioplasty, bleeding at the femoral artery access site accounted for most serious bleeding events and occurred more often in the Integrilin- than placebo-treated groups. The incidence of serious non-bleeding adverse events was similar among Integrilin- and placebo-treated patients.

The most common serious adverse events are summarized in table 6-18.

Table 6-18
Serious Adverse Events Occurring at Any Time

Adverse Event	Coronary Angioplasty				Unstable Angina				Total			
	Integrelin (N=2763)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	%	N	%	N	%	N	%	N	%	N	%
Any Serious Adverse Event	917	33.5	453	33.6	18	8.9	6	5.6	935	31.8	459	31.5
Any Serious Bleeding Event	196	7.2	85	6.3	9	4.4	1	0.9	205	7.0	86	5.9
Femoral Artery Access Site	132	4.8	50	3.7	0	0	0	0	132	4.5	50	3.4
CABG-Related	41	1.5	28	2.1	1	0.5	0	0	42	1.4	28	1.9
Serious Non-Bleeding Adverse Event												
Any Whole Body System	41	1.5	22	1.6	0	0	0	0	41	1.4	22	1.5
Any Cardiovascular System	763	27.9	398	29.5	12	5.9	5	4.7	775	26.4	403	27.7
Chest Pain / Angina	695	25.4	355	26.3	2	1.0	0	0	697	23.7	355	24.4
Myocardial Infarction	82	3.0	54	4.0	6	3.0	3	2.8	88	3.0	57	3.9
Any Nervous System	35	1.3	23	1.7	1	0.5	0	0	36	1.2	23	1.6
Stroke	16	0.6	8	0.6	1	0.5	0	0	17	0.6	8	0.5
Thinking Abnormality	10	0.4	4	0.3	0	0	0	0	10	0.3	4	0.3
Any Respiratory System	33	1.2	18	1.3	0	0	0	0	33	1.1	18	1.2
Respiratory Distress	14	0.5	9	0.7	0	0	0	0	14	0.5	9	0.6

4.0 Clinical Laboratory Evaluation:

Four potential areas of concern based on results from preclinical studies and the known action of Integrilin were studied in details: decrease in platelet count and thrombocytopenia; decrease in hematocrit and/or hemoglobin related to bleeding events; liver function; and renal function. However, all laboratory parameters were included in the ISS database and reviewed for evidence of Integrilin-related effects. Other than decreases in hemoglobin and hematocrit in Integrilin-treated patients consistent with the increase in minor bleeding, there was no other evidence of treatment related changes found during analysis of any laboratory parameter. No differences across the various populations were observed.

4.1 Clinical Laboratory Parameters: Baseline means and maximum mean changes from baseline for hemoglobin and hematocrit for the ISS database are summarized in Tables 7-1 and 7-2.

Table 7-1

Mean at Baseline and Mean Change from Baseline for Hemoglobin

Hemoglobin (g/dl)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2651	1299	199	102	2850	1401
Mean	13.9	13.9	13.2	13.4	13.9	13.9
SD	1.48	1.46	1.82	1.62	1.51	1.48
Range						
Maximum Change from Baseline*						
N	2605	1273	197	101	2802	1374
Mean	-1.2	-1.0	-0.8	-0.7	-1.1	-1.0
SD	2.13	1.97	1.41	1.26	2.09	1.92
Range						

* Or first time point after treatment termination

Table 7-2

Mean at Baseline and Mean Change from Baseline for Hematocrit

Hematocrit (%)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2651	1299	198	102	2849	1401
Mean	41.0	41.0	39.0	39.5	40.8	40.9
SD	4.18	4.17	5.04	4.51	4.28	4.21
Range						
Maximum Change from Baseline*						
N	2606	1273	196	101	2802	1374
Mean	-3.3	-2.9	-2.2	-2.2	-3.2	-2.9
SD	5.50	5.52	4.30	3.75	5.43	5.41
Range						

* Or first time point after treatment termination

Overall, there was no evidence of a drug-related effect on platelet counts. Significant decreases in platelet counts occurred with similar frequency in Integrilin- and placebo-treated groups.

Although thrombocytopenia as a subjective report was "more frequent" with Integrilin than placebo in the IMPACT II study (0.6% vs 0.2% vs 0% in the high-dose, low-dose, and placebo groups, respectively), examination of laboratory data (nadir counts, proportion of patients with counts less than 100,000/mm^3 or less than 50,000/mm^3) failed to reveal objective evidence of a real difference in platelet counts between active drug and placebo during infusion and afterward until patients left the hospital.

The mean baseline platelet counts and mean changes from baseline for platelets are summarized in table 7-3 and the marked abnormalities for platelet by treatment are summarized in table 7-4.

Table 7-3

Mean at Baseline and Mean Change from Baseline for Platelets

Platelets (K/mm3)	Coronary Angioplasty Studies		Unstable Angina Studies		Total	
	Integrelin	Placebo	Integrelin	Placebo	Integrelin	Placebo
Baseline						
N	2649	1297	198	101	2847	1398
Mean	235.0	234.5	255.5	249.0	236.4	235.5
SD	63.18	63.82	81.02	63.22	64.77	63.87
Range						
Maximum Change from Baseline*						
N	2645	1293	197	101	2842	1394
Mean	-8.2	-10.9	-16.6	-14.7	-8.8	-11.2
SD	70.0	72.75	64.81	46.62	69.67	71.17
Range						

* Or first time point after treatment termination

Table 7-4

Summary of Marked Abnormalities for Platelets by Treatment Group

Post-Baseline Platelet Abnormality	Coronary Angioplasty				Unstable Angina				All Studies			
	Integrelin (N=2736)		Placebo (N=1348)		Integrelin (N=203)		Placebo (N=107)		Integrelin (N=2939)		Placebo (N=1455)	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<100,000/mm^3	71	(2.6)	31	(2.3)	3	(1.5)	0		74	(2.5)	31	(2.1)
50% drop from BL	62	(2.3)	38	(2.8)	2	(1.0)	1	(0.9)	64	(2.2)	39	(2.7)
<50,000/mm^3	7	(0.3)	8	(0.6)	0		0		7	(0.2)	8	(0.5)

There was no evidence of a drug-related effect of Integrilin on LFTs. Mean and median values of SGOT and SGPT, changes from baseline and marked abnormalities were similar for Integrilin- and placebo-treated groups.
No significant abnormalities were noted for alkaline phosphatase

There was no evidence of an effect of treatment with Integrilin on renal function.

4.2 Immunogenicity of Integrilin: The potential for this disulfide-linked cyclic heptapeptide to produce an immune response in humans was addressed in three separate clinical studies in a total of 390 patients. Protocol 94-019, designed to specifically study the development of anti Integrilin antibodies and allergic reactions with repeat exposure, was conducted in 28 healthy volunteers under randomized, double-blinded, placebo-controlled conditions. Twenty-one subjects received a bolus dose and infusion of Integrilin on two separate occasions separated by one month. Follow-up examinations for the presence of anti-Integrilin antibodies were conducted up to 16 weeks after the initial exposure.
In Protocol 92-009, 22 patients had blood samples drawn for the detection of antibodies to Integrilin at baseline and at the 30-day assessment.
In the IMPACT II Study, the first ten patients enrolled at each site were tested for the presence of Integrilin antibodies at the 30-day assessment.

There was no evidence of immunogenic response to Integrilin: no anti-Integrilin antibodies were detected in 390 patients and no serious adverse events occurred with repeat administration of Integrilin 30 days apart. Repeat dosing gave similar plasma drug concentrations and inhibition of platelet aggregation.

5.0 Drug Interactions

5.1 Drug-Drug Interaction: No evidence of a pharmacokinetic interaction was observed in Phase I and II studies with the administration of Integrilin plus ASA and/or heparin. Simplate bleeding times were modestly increased in the presence of Integrilin, heparin had no additive effect.
A population pharmacokinetics study was conducted within the IMPACT II study, where 1725 treated patients had a single plasma Integrilin concentration determined prior to terminating the infusion. Although plasma Integrilin clearance appeared to be affected by age, weight and renal function, it was not found to be affected by the co-administration of any of the cardiac drugs which were coadministered during the study, and which represent the medications most likely to be administered in the target population, including beta-blockers, calcium channel blockers, diuretics, heparin.

The effect of concomitant administration of other known antithrombotic agents was examined in detail in the IMPACT II study. Table 10-2 summarizes major and minor bleeding events by concomitant medications.

Table 10-2

Incidence of CEC-Adjudicated Major and Minor Bleeding by Subgroup* and Treatment Group in the IMPACT II Study

CEC Bleeding By	Integrelin High Dose		Integrelin Low Dose		Placebo	
	Major	Minor	Major	Minor	Major	Minor
Warfarin	12/105 (11.4%)	26/105 (24.8%)	13/130 (10.0%)	27/130 (20.8%)	17/153 (11.1%)	44/153 (28.8%)
No Warfarin	46/1140 (4.0%)	151/1140 (13.2%)	42/1119 (3.8%)	119/1119 (10.6%)	38/1077 (3.5%)	71/1077 (6.6%)
Warfarin and PT ≤14.5 sec	11/96 (11.5%)	25/96 (26.0%)	10/114 (8.8%)	25/114 (21.9%)	14/127 (11.0%)	37/127 (29.1%)
Warfarin and PT >14.5 sec	0/4 (--)	0/4 (--)	2/9 (22.2%)	1/9 (11.1%)	0/14 (--)	4/14 (28.6%)
Dipyridamole	17/189 (9.0%)	38/189 (20.1%)	14/180 (7.8%)	33/180 (18.3%)	18/191 (9.4%)	35/191 (18.3%)
No Dipyridamole	41/1056 (3.9%)	139/1056 (13.2%)	41/1069 (3.8%)	113/1069 (10.6%)	37/1039 (3.6%)	80/1039 (7.7%)
Thrombolytics	1/15 (6.7%)	4/15 (26.7%)	2/15 (13.3%)	4/15 (26.7%)	2/23 (8.7%)	5/23 (21.7%)
No Thrombolytics	57/1230 (4.6%)	173/1230 (14.1%)	53/1234 (4.3%)	142/1234 (11.5%)	53/1207 (4.4%)	110/1207 (9.1%)

* In each category, denominator is total number of patients with CEC bleeding status determined.

5.2 Drug-Demographic Interaction: In the IMPACT II study, an increase of 10 kg in weight from the median of 84 kg was associated with an increase of 5.9% in the estimated mean plasma Integrilin clearance of 158 mL/min. Also, an increase of 10 years in age from the median of 60 years was associated with a 5.3% decrease in Integrilin clearance.

In the younger subjects enrolled in most Phase I studies, estimates for plasma clearance were also consistently higher and had a half-life shorter compared to the older patients enrolled in Phase II studies or the four healthy, but older, post-menopausal women studied in Phase I.

The population pharmacokinetics analysis in IMPACT II did not reveal any notable influence of gender, inadequate data were available for non-Caucasian to assess the influence of ethnic origin. Major bleeding was inconsistently correlated with increasing age, except that the highest incidence was noted in patients > 70 years of age in the high dose Integrilin group (7.1%). Minor bleeding was correlated with increasing age, and older patients treated with Integrilin were at higher risk compared to placebo treated patients. Patients weighing < 74 kg had an increased incidence of minor bleeding and this risk was increased by Integrilin. In the high

dose Integrilin group, patients weighing < 74 kg also had an increased incidence of major bleeding. Women had an increased incidence of minor bleeding compared to men, and this risk was increased by Integrilin. Women in the high dose Integrilin group also had an increased risk of major bleeding. Part of this risk is attributable to weight differences between men and women.
Overall, there was no consistent evidence of a difference in the effect of Integrilin relative to placebo among the subgroups for non-bleeding adverse events.

5.3 Drug-Disease Interaction: In the IMPACT II study, one of the patients with creatinine >2.0 mg/dL in the high dose group experienced an intracranial bleed during the infusion period. The patient had also uncontrolled hypertension. Other adverse events experienced by this group of patients were similar to those of the general patient population. Additionally, there were no clinically relevant changes in laboratory values following treatment for these patients.

Integrilin is intended as an acute-care product (up to 72 hours of exposure), no long-term use is anticipated. Due to the short half-life of Integrilin (about 2 hours), no long-term adverse effects are expected to be associated with treatment.

6.0 Dosing Safety

The number of patients and adverse event rates in Phase I and Phase II studies not included in the ISS database were too low to allow meaningful conclusions regarding the relationship between drug exposure and adverse events.
The vast majority of patients included in the ISS analysis are derived from the 94-014 (IMPACT II) study.

Table 13-1 shows the occurrence of bleeding by cumulative exposure to Integrilin.

Table 13-1
Bleeding Events by TIMI Criteria by Cumulative Dose in ISS Database

TIMI Classification	Total Cumulative Dose of Integrelin (µg/kg)									
	≤ 700		700-850		850-1000		1000-1150		≥ 1150	
	N	%	N	%	N	%	N	%	N	%
Major	58	14.6	19	2.2	12	2.8	17	3.0	18	2.9
Minor	88	22.2	86	10.0	47	11.1	66	11.5	73	11.8
Insignificant	118	29.7	428	49.8	216	50.9	292	51.0	268	43.3
None	119	30.0	290	33.7	136	32.1	183	31.9	249	40.2

The expected cumulative drug exposures for a 20-24 hour infusion (including bolus) are 735-855 µg/kg and 1035-1215 µg/kg for the 0.5 µg/kg-min and 0.75 µg/kg-min groups, respectively.

The cumulative dose represents a measure of the dose level (0.5 mg/kg-min versus 0.75 mg/kg-min) and the duration of the infusion. The greater frequency of major and minor bleeding events or non-bleeding events in patients having received $\leq$700 ug/kg of drug likely reflects its premature discontinuations presumably due to bleeding or other adverse events, rather than an inverse relationship between dose and bleeding frequency. Greater cumulative exposures to Integrilin were not associated with a greater incidence of bleeding event.

6.1 Overdose: This included large bolus doses, rapid infusion reported in the CRF as "overdose", and large cumulative doses. None of the three patients receiving large bolus dose had significant adverse events or changes in laboratory values. There were 10 reports of accidental "overdosage" in the IMPACT II study, 8 in the Integrilin groups (5 high dose, 3 low dose) and 3 in the placebo group. None of these patients received twice the recommended bolus dose or infusion rate. None of these patients had a serious adverse event or more than mild bleeding (usually at the access site). Plasma levels of Integrilin, available for 7 of the 8 patients, were similar to the mean levels for patients dosed properly. Two patients in the high-dose Integrilin had high plasma levels after receiving rapid infusion rates, with no apparent effect. The safety profiles of 3 patients who received a total cumulative dose of over 5000 mg/kg showed no adverse events or laboratory values.

6.2 Withdrawal Effects: Because Integrilin is intended for use a an acute-care product, effects of withdrawal are not anticipated. Adverse events in the IMPACT II study reported as occurring between 24 hours post-treatment and 30 days post-randomization were similar between Integrilin-treated and placebo-treated patients. There are no known effects of withdrawal associated with the use of Integrilin.

7.0 Safety Update (4 month)

A 4 month safety update was submitted on 8-2-1996. No additional studies in PTCA patients had been performed. One Phase III study in UA (PURSUIT) is ongoing and still blinded. One Phase II study in acute MI has been completed, but the final analysis is not yet completed. Both studies employed dose regimens of Integrilin different from those used in the IMPACT II study. The data reported for the safety update reflect the different dose regimens and the different patient populations, however, no unexpected adverse events were reported.

CONCLUSIONS

Integrilin is a cyclic peptide with selective and reversible binding affinity to the GPIIb/IIIa platelet receptor complex. Integrilin inhibits platelet aggregation independently of the inducing mechanism because it prevents the ultimate, common pathway of fibrinogen binding to the platelet receptor GPIIb/IIIa. The effect of Integrilin on platelet is immediate, rapidly reversible and limited primarily to the period of its administration. Integrilin has been developed as an antithrombotic agent for the treatment of acute coronary syndromes where local thrombus formation plays a major pathogenetic role.

A New Drug Application (NDA 20-718) has been submitted by COR Therapeutics, Inc. for the approval of Integrilin as an adjunct therapy in patients undergoing percutaneous transluminal coronary angioplasty, atherectomy, excimer laser or rotoblator (PTCA) for the prevention of acute cardiac ischemic complications (death, MI, need for urgent intervention) related to abrupt closure of the treated coronary vessel.

A single adequate and well controlled Phase III clinical trial, the IMPACT II study, has been submitted in the NDA to provide substantial evidence of the efficacy and safety of Integrilin in preventing the acute ischemic complications of coronary angioplasty. IMPACT II is a large, randomized, multi-center, double-blind clinical trial of 4010 patients undergoing urgent or elective PTCA at 83 centers in the US. The study design had minimal exclusion criteria allowing a broad cross-section of the population to be studied. The large study population adequately represented the target population for the proposed indication. Randomization and blinding to treatment assignment were adhered to throughout the study. Some discrepancies in the data reported in the NDA were noted during the review, however, they did not seem to affect the final interpretation of the study results. The results were not determined by any study center in particular and there was no evidence of selection bias.

Two dosing regimens of Integrilin, 135 ug/kg bolus followed by infusion of 0.75 ug/kg/min for 20-24 hours and 135 ug/kg bolus followed by 0.50 ug/kg/min infusion for 20-24 hours (referred to as "high-dose" and "low-dose", respectively,) were each compared to placebo, allowing for internal replication of results.

The primary efficacy endpoint specified in the study protocol was the composite occurrence of death, myocardial infarction and/or urgent coronary intervention. The components of the composite endpoint were adjudicated by an independent, blinded clinical events committee (CEC) according to protocol-

specified definitions. Clinical events were also evaluated according to the investigators' assessment as reported in the CRFs.

The primary assessment was at 30 days from randomization in order to determine whether the benefits from Integrilin administration were sustained beyond the periprocedural period. Efficacy was also assessed at 24 and 48 hours from randomization when the risk of abrupt closure and acute ischemic events is highest. Pre-specified secondary endpoints included rates of abrupt closure and clinical events at 6 months.

Two pre-specified data sets were analyzed: the randomized and the treated patient populations. A total of 139 from the 4010 randomized patients (3.5%) did not receive study medication because randomization was assigned before the eligibility of the patient was established or before the decision to treat the patient or to proceed with angioplasty could be made by the investigator. These 139 untreated patients were evenly distributed across the three study groups, were randomized at more than half of the study centers and were excluded from treatment by investigators who were blinded to treatment assignment. For the above reasons, the "treated patient" population was considered valid for the primary efficacy analyses. A "randomized patient" analysis was performed as well in order to provide supportive information and to check for potential selection bias.

The protocol-defined level of significance for the comparison of the composite clinical endpoint between each Integrilin group and placebo was set at the p-value $=0.035$ in order to adjust for dual pair-wise comparisons and, more importantly, for the interim analyses performed during the study. However, when fully adjusted, the p-value of 0.035 actually corresponded to an overall alpha level of 0.067. The conventional p-value of 0.05 was used for all other comparisons in this study.

The efficacy results of the IMPACT II study showed that the administration of Integrilin to patients undergoing PTCA produced a marked reduction in the incidence of acute ischemic events when compared to placebo at 24 hours post-PTCA. Both dosing regimens of Integrilin effectively reduced the incidence of the composite endpoint of death, MI and/or urgent revascularization by 28-31% compared to placebo. The reduction persisted for approximately 5 days after PTCA without evidence of rebound thrombotic events after discontinuation of study drug. In the early post-angioplasty period of greatest risk, more placebo patients discontinued study drug because of coronary occlusion than Integrilin-treated patients. The incidence of abrupt closure was reduced by 35% ($p=0.030$) in the high dose Integrilin group and by 45% ($p=0.003$) in the low dose Integrilin group compared to placebo. As expected, abrupt closure had a very high incidence of

ischemic events (>40%) compared to 10% for patients without abrupt closure.

At 30 days post-PTCA, a reduction in incidence of the composite endpoint persisted in the Integrilin groups compared to the placebo group. However, the reduction was statistically significant only In the low dose Integrilin-treated group at the nominal p-value=0.035. In this group, the risk reduction of ischemic events was 21.6% with an absolute reduction of composite endpoint of 2.5%.
No statistically significant difference was found in the high-dose Integrilin due to the occurrence of 6 additional composite endpoint between day 5 and 30 in this group compared to placebo, nor in the randomized population due to 5 composite endpoint events: 1 in the high dose group and 4 in the low-dose group.

The long-term effect of Integrilin was also assessed at 6 month post-randomization. As most revascularization procedures performed after 30 days from randomization in all treatment groups were elective, the 6-month analysis examined the composite of death and/or MI and a composite of death, MI and/or any (i.e. urgent and non-urgent) intervention. A numerical reduction in the composite endpoint events of death and MI persisted at 6 months in the Integrilin-treated patients compared to placebo. The net difference in incidence of the composite endpoint of death and MI compared to placebo was 1.3% for the low-dose and 1.6% for the high-dose Integrilin regimen.
Elective or non-urgent coronary revascularization procedures were performed throughout the study period up to 6 months post-randomization. The relative risk reduction of all events (death, MI and any revascularization procedure) in the low-dose group compared to placebo was 21.2% at 24 hours, 12.1% at 30 days, and 4.0% at 6 months. More Integrilin-treated patients had required re-hospitalization because of chest pain/angina than patients in the placebo group.

Several additional efficacy analyses were performed, including the analysis of the investigator assessed endpoints, a post-hoc comparison of the combined Integrilin treatment groups to placebo, analyses of first or most severe endpoint events, high or low risk stratification, MI subtypes, effect of investigational site.

The 30 day efficacy analysis performed according to the investigators' assessment of the composite endpoint events showed a statistically significant difference in favor of the low-dose Integrilin compared to placebo in both treated and randomized patient populations. However, the investigators and the CEC analyses were discordant in that the investigators identified considerably fewer clinical events, particularly MIs, than the CEC. The MI were classified by the CEC as Q-wave MI and small or large enzyme MI according to ECG findings and degrees of elevations of CK/CK-MB levels. The CEC identified more MIs on the basis of elevated post-angioplasty CK and CK-MB levels. Although the investigators

concurred with the CEC for the identification of large enzyme MI more frequently than for the identification of small enzyme MI, a considerable proportion of large enzyme MI were not identified by the investigators (36/53 in the high-doe group, 29/52 in the low-dose group, and 39/68 in the placebo group).

A comprehensive analysis of the results was performed to examine any patient subgroup that may experience a greater or lesser therapeutic effect from Integrilin. A numerical difference in favor of Integrilin was detected in a wide variety of subgroup analyses of efficacy. Of note is that no Integrilin-treated patient populations were identified who experienced a worse clinical outcome than the placebo group. No gender-related differences in efficacy were noted.

Sub-group analyses by risk level, stent placement, and concomitant aspirin and heparin therapy were also performed.

Integrilin-treated patients undergoing low-risk or elective PTCA (as determined by the randomization questionnaire, by the investigator assessment in CRFs, and by the EPIC criteria) experienced fewer events than patients in the high-risk stratum. However, the prospectively defined risk stratification was not predictive of outcome because no difference in incidence of events was observed between the high- and low-risk strata in the placebo-treated group at either 24 hours or 30 days.

A total of 91 patients underwent PTCA with placement of stents and continued Integrilin therapy during stent placement having been randomized to either Dextran/placebo-Integrilin or to Integrilin/placebo-Dextran. The incidence of the primary composite endpoint at 30 days for patients receiving stents was lower in the Integrilin groups than in the placebo group.

Most patients in IMPACT II received concomitant aspirin and heparin to reduce the risk of acute cardiac complications due to thrombosis. All patients in the study received at least one bolus of heparin. No consisted effect of heparin therapy duration was observed on the incidence of composite endpoint.
In the small group of patients (n=80) who did not receive aspirin due to a contraindication, the incidence of the composite endpoint was lower in the Integrilin-treated patients.

The overall safety profile of Integrilin, at the dose regimens used in the clinical trials in the NDA, was favorable. As expected, bleeding was the most commonly reported adverse event. The great majority of bleeding events occurred at the femoral artery access site as a result of the angioplasty procedure itself. Most of the bleeding events were minor and limited to the period during which the patient was being treated. Minor bleeding was, however, more frequent with Integrilin that with placebo; a dose-response was also apparent for minor bleeding.

Moderate bleeding, including spontaneous bleeding, was more frequent in patients receiving Integrilin. In fact, more Integrilin-treated patients than placebo patients discontinued study drug due to bleeding complications.
Severe bleeding events as defined by TIMI criteria and by investigator assessment were rare and occurred with equal frequency in all groups. The overall incidence of intracranial bleeding with Integrilin was low and not higher than with placebo.
Major bleeding associated with CABG surgery was actually less common among patients receiving Integrilin.
In general, the incidence of major and minor bleeding events increased in females and with increasing age and lower body weight. Patients receiving concomitant warfarin and/or dipyridamole experienced an increased incidence of major and minor bleeding events, but Integrilin did not increase this risk.

Adverse events other than bleeding that occurred more often in the Integrilin-treated patients compared to placebo, were back pain, hypotension (secondary to bleeding) and pain at the injection site.

There was no evidence of Integrilin-related organ toxicity (liver, kidney).
No adverse hematological effects, other than reduction in Hgb and Hct secondary to blood loss were detected in the Integrilin-treated patients. Inhibition of platelet aggregation induced by Integrilin does not appear to affect the viability of platelets, as demonstrated by the low overall incidence of reported thrombocytopenia, which occurred with similar frequency in all treatment groups.
The potential for thrombocytopenia was of specific concern because of the findings in one animal study of a transient dose-dependent decrease in platelet counts in female rabbits which was not reproduced in other animal studies.

Allergic reactions were rare and occurred with similar frequency in the Integrilin and placebo groups. There were no cases of anaphylaxis and no antibodies to Integrilin were detected in 412 patients 30 days after one administration and in 21 patients after repeated administrations of Integrilin.

It is of note that in IMPACT II only 44.5% of the patients in the Integrilin low-dose group (50 ug/kg-min) group and only 68.3% of the patients in the Integrilin high-dose group (0.75 ug/kg-min) had a steady-state plasma concentration of Integrilin which would have resulted in at least an 80% inhibition of ADP-induced *ex vivo* platelet aggregation. A higher dose regimen of Integrilin might reduce further the incidence of ischemic events, however, the likelihood of more clinically significant bleeding would negatively affect the risk/benefit relationship of the treatment.

In conclusion, Integrilin exhibited a marked antithrombotic effect which significantly reduced the risk of abrupt closure and related complications in the early post-PTCA period. A marginal reduction of the composite endpoint of ischemic events was sustained at 30 days in the low-dose (135 ug/kg bolus followed by a 0.5 ug/kg/min infusion of 20-24 hours) Integrilin-treated group. The clinical importance of Integrilin as an adjunct therapy for the prevention of acute ischemic complications related to abrupt closure in patients undergoing coronary angioplasty will be evaluated by the Cardio-Renal Advisory Committee.

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