

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-718**

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW**NDA 20-718****DRUG:** eptifibatide (Integrilin®)**SPONSOR:** COR Therapeutics**TYPE OF SUBMISSION:** Resubmission of Non-approved NDA**DATES OF SUBMISSIONS:** 9/30/97, 10/23/97**REVIEWER:** Ameeta Parekh, Ph.D.

Eptifibatide (Integrilin) is a synthetic cyclic heptapeptide which binds competitively to the glycoprotein (GP) IIb/IIIa receptor complex, thus inhibiting platelet aggregation by preventing the binding of fibrinogen and other ligands to GP IIb/IIIa. NDA 20-718 was previously reviewed by the Agency (HFD-180) for the prevention of acute cardiac ischemia complications in patients undergoing Percutaneous Transluminal Coronary Angioplasty (PTCA) where integrilin was intravenously administered adjunct to aspirin and heparin. The doses investigated in the clinical trial were 135 ug/kg bolus plus 0.5 or 0.75 ug/kg/min infusion over 24 hours. The NDA was discussed at the Cardio-Renal Advisory Committee Meeting (February, 1997) and the panel concluded that the singular clinical trial (IMPACT II) was not sufficiently robust to support approval, even though the trial indicated drug activity. A non-approvable letter was issued on 3/21/97 which, in addition to stating the clinical deficiencies, pointed out to the sponsor that the analytical methodology for determination of integrilin in pharmacokinetic (PK) studies was lacking with respect to assay validation and therefore could provide only qualitative information for this section. The application has since been transferred from HFD-180 to HFD-110. The NDA is being resubmitted with an additional clinical trial (PURSUIT) where 180 ug/kg bolus integrilin with infusions of either 1.3 or 2 ug/kg/min were tested (the lower infusion was subsequently dropped from the trial due to lack of safety with the higher dose). The increase in dose in the second clinical trial, PURSUIT, was based on measurements of platelet inhibition activity of integrilin using sodium citrate and PPACK as anticoagulants. Use of the former (used in dose determination in IMPACT II) was reported to overestimate the activity of integrilin compared to PPACK for the targeted platelet inhibition of 80% of baseline (Figures 1-3). Additionally, reports from 5 clinical pharmacology and PK studies have been submitted which are addressed in this review.

SYNOPSIS:

The clinical pharmacology studies conducted by the sponsor during the Phase I and Phase IIa stages of drug development were primarily targeted at finding an appropriate dose that would provide adequate (80% of baseline) inhibition of platelet aggregation (ex-vivo measurements) for the clinical trial, IMPACT II, in PTCA patients. Integrilin was administered in the trial as an i.v. bolus followed by an infusion over 24-72 hours. The primary end-points for the drug efficacy was mortality benefit, reduction in myocardial infarction or reduction in revascularization.

In the original application, integrilin PK and pharmacodynamics (PD) were assessed after i.v.

bolus and infusion administrations of integrilin to normal volunteers, post-menopausal women, moderate renal dysfunction patients and coronary artery disease (CAD) patients undergoing PTCA. Bolus doses ranged from 20-180 ug/kg and infusions ranged from 0.2 to 1.5 ug/kg/min lasting for 90 minutes to 24 hours. Aspirin and heparin were coadministered in some studies. Quantitation of PK parameters was limited due to inadequate assay validation, however, some general qualitative assessments are possible.

Dose-proportionality (with respect to relative plasma levels) can be concluded over the range of doses studied. Plasma $t_{1/2}$ ranged from 2-3 hours and the PK parameters were not influenced by presence of aspirin or heparin. Bolus administration followed by infusion was considered necessary to achieve instantaneous high concentrations. Bolus doses higher than 90 ug/kg bolus dose were considered adequate to provide these concentrations. Plasma clearance (CL) and volume of distribution (V_{ss}) were reported

however, the accuracy of these parameters is questionable due to assay deficiencies. A subset of IMPACT II (135 ug/kg followed by infusion of 0.5 ug/kg/min or 135 ug/kg bolus followed by 0.75 ug/kg/min infusion over 20-24 hours) patients with one plasma sample per patient prior to the termination of infusion were assessed in a population PK setting. This analysis revealed that weight, creatinine clearance and age are significant covariates for the PK parameters of integrilin, with clearance being proportional to weight and renal status and inversely related to age. Integrilin is eliminated, at least in part by renal excretion with the primary degradation product found in human urine to be deamidated integrilin (D-in). The latter has about 41% of the IPA activity as integrilin. The D-in is shown to be formed in urine ex-vivo, and possibly within the bladder in man. The metabolic pathways were not adequately characterized. Protein binding was 24% at concentrations ranging from 0.05-15 ug/ml indicating medium to high unbound fraction of about 0.75.

The early studies used sodium citrate as the anticoagulant. The clinical pharmacology measurements, Simplate Bleeding Time, SBT, and inhibition of platelet aggregation, IPA, (10, 20 or 50 uM ADP induced), were determined frequently during integrilin administrations and these assessments help corroborate some of the clinically relevant features of this drug. Neither aspirin nor heparin influenced the PA; integrilin had a significant inhibitory effect that lasted during the infusion period and PA reverted back to baseline within about 6 hours of infusion termination. Integrilin effect on IPA was dose and duration of infusion related, with >90% inhibition achieved with short infusions (90 min) of 1-1.5 ug/kg/min. With 0.5 ug/kg/min infusion over 6 hours, near complete IPA was achieved by 4-6 hours. Note that steady state concentrations were not achieved during this period yet the maximum IPA was approached with respect to E_{max} . This may suggest that concentrations or doses higher than these may prolong the time taken to return to baseline but may not add to the benefit (IPA) of the drug. The IPA potential of integrilin was not influenced by either aspirin or heparin. SBT was maximal with aspirin (3 fold higher than baseline). Heparin and 0.5 ug/kg/min integrilin over 90 minutes had minimal effect on SBT. Infusions over 6 hours or doses higher than 0.5 ug/kg/min showed 2 fold increases in SBT as compared to baseline. A combination of aspirin, heparin and integrilin (0.5 ug/kg/min over 6 hours) showed about 5-6 fold increase in SBT. Postmenopausal women, moderate renal patients and CAD patients showed similar PK and PD trends to normal subjects.

The Clinical Pharmacology and Biopharmaceutics Section of the resubmitted NDA consists of data from five additional studies in which a validated LC/MS assay has been used for the detection of integrilin and D-in in plasma and urine. These studies are:

1. Study 96-021: ¹⁴C-integrilin mass balance study in healthy volunteers
2. Study 96-028: PK/PD study after iv bolus doses in healthy volunteers
3. Study 26-029: PK/PD study after continuous 24 hour iv infusions in healthy volunteers
4. Study 94-016a (PERIGEE): PK/PD study (substudy of PURSUIT, a pivotal trial in patients with unstable angina/non Q-wave myocardial infarction, UA/NQMI).
5. Study 96-023 (PRIDE): PK/PD study in patients undergoing coronary angioplasty.

The following summarizes the amended studies (details of each study are provided in the appendix).

Integrilin disposition after a bolus dose is characterized by a bi-exponential decay with t_{1/2} of 0.08 and 1.1 hours respectively. Steady state was achieved in plasma in about 6 hours after start of infusion. The mean clearance was 9.6 L/hr (160 ml/min), suggesting that integrilin is a low extraction drug, V_c was about 9 L and V_{ss} was about 16 L. Plasma concentrations of D-in were negligible. C_{ss} and AUC increased in a dose proportional manner. Integrilin accounted for more than 80% of the radioactivity seen in plasma. Plasma radioactivity was higher than whole blood. Recovery of radioactivity over 72 hours was about 73% with 71.4% of dose recovered in urine (36% and 25% as integrilin and D-in) and approx 1.1% and 0.0001% in feces and breath, respectively. This indicates that drug derived radioactivity was retained beyond 72 hours which is supported by the long terminal t_{1/2} for total radioactivity of about 15 hours. Recovery could have been higher with a prolonged collection period. Cl_r (renal clearance) of about 65 ml/min is lower than GFR*fu (120*0.75) which suggests that integrilin may be reabsorbed from tubules or it may be underestimated due to D-in formation in the bladder. Note that the long t_{1/2} of total radioactivity could raise concerns with respect to accumulation with long term infusions. Safety or efficacy however, was not a concern with these infusions. Following discontinuation of infusion platelet activity reverted back to baseline within 4-6 hours

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Study	028*			029**			021*	016A*/**	023*/**		
Dose	90	135	180	0.5	1	2	135	180/2	135/.75	180/2	250/3
C _{ss} (ng/ml)	-	-	-	265	525	1058	-	2201	724	1499	2351
t _{1/2} (hr)	1.53	1.35	1.59	2.31	2.42	2.38	1.13	2.77	2.46	2.8	2.6
V _{ss} (ml/kg)	230	220	240	270	260	260		185	201	259	238
V _c (ml/kg)							121				
Cl (ml/kg.hr)	131	130	123	114	115	114	128	55	62	80	76

* bolus dose, ug/kg, ** infusion dose, ug/kg/min

Pharmacodynamic parameters measured were bleeding time and platelet aggregation. Platelet aggregation was determined using using 2 anticoagulants (sodium citrate and PPACK, since there is a suggestion that sodium citrate overestimates the integrilin response).

Comparison of platelet aggregation with sodium citrate and PPACK as antocoagulants shows a dose related IPA for both. Inhibition was higher with sodium citrate but with both anticoagulants, baseline values were achieved in about 4 hours after infusion termination.. IC50 and IC80 values were higher (nearly double) for determinations with PPACK collected blood, as compared to sodium citrate.

With bolus doses of 90-180 ug/kg, SBT was approximately 1.5-2 fold higher and it increased in a dose dependent fashion. Bleeding time increased to nearly 5 fold with the high infusion rate of 2 ug/kg/min.

COMMENTS TO THE MEDICAL OFFICER:

- Note that the steady state concentrations achieved with infusions of 2 ug/kg/min exceed 1000 ng/ml. Pharmacodynamic assessment of these high concentrations (Figure 3) suggest that E_{max} is achieved with respect to IPA by about 1000 ng/ml. Higher concentrations, from higher doses, may not add to the benefit with respect to IPA. This should be taken into consideration for dose selection.
- Although inhibition of platelet aggregation by integrilin was not influenced by heparin or aspirin, bleeding time was increased 5-6 fold. Consequences of coadministration of these drugs should be appropriately addressed in the labeling.

LABELING COMMENTS:

- PHARMACOKINETICS section of the labeling currently states "The expected changes in eptifibatide steady state plasma concentrations are modest and correspond to an increase of about 20% from age 40 to 80 an increase of about 4-5% for each 10 ml/min decrease in

creatinine clearance, and a decrease of about 25% between 60 kg and 100 kg body weight. Since these parameters have only modest effects on plasma eptifibatide levels, no dose adjustment is required based on age, weight or renal function up to serum creatinine of 2.0 mg/dl.”

There may be compounded factors of these demographic characteristics in patients and an overall effect on plasma concentrations may be higher. Therefore, the last statement “no dose adjustment...” should be deleted from this section. Based on Medical Review (Isaac Hummond, M.D.), patients above 75 years of age and weighing less than 60 kg were susceptible to excessive bleeding. Appropriate dosing recommendation should be considered in the DOSAGE AND ADMINISTRATION section.

2. The clearance in patients with coronary artery disease is reported to be 55 to 80 ml/kg.min in the PHARMACOKINETICS section of the label. The following statement should be added “The clearance is two fold higher in normal subjects”.

3. “...bleeding time returning toward baseline within 2 hours”. Platelet aggregation reverts back to baseline in 4-6 hours. Is there data for bleeding time returning to baseline in 2 hours? If so, the dose should be specified.

4. Under PRECAUTIONS, the label states regarding Renal Insufficiency “...no dose adjustment is required based on renal function unless serum creatinine levels exceed 2.0 mg/dl or a patient is undergoing renal dialysis.” Since the drug is 25% protein bound, it may clear with dialysis. If severe renal deficiency patients or dialysis patients have not been studied, label should clearly state this. The present statement in the label is ambiguous and does not help with dosage adjustment.

5. DRUG INTERACTIONS sections states that there was no PK interaction with several drugs based on a population PK study in IMPACT II. Note that the assay was deficient in this study and the number of patients using coadministered drugs may be small to conclusively rule out the possibility of an interaction. Unless this can be conclusively ruled out, this statement should be deleted from the label.

6. DOSAGE AND ADMINISTRATION section should address the precautions in renal patients, elderly, low weight and patients on dialysis.

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RECOMMENDATION:

The pharmacokinetics and clinical pharmacology section of NDA 20-718 has been reviewed by DPE I. The comments to the Medical Officer and the specific labeling recommendations listed above should be taken into consideration. The data submitted in the NDA appropriately address this section and is acceptable.

Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation I

3/5/98

FT Initialed by Ahmed El-Tahtawy, Ph.D. : _____
cc: NDA 20-718, HFD-110(McDonald), HFD-860 (Parekh), CDR (Attn: Barbara Murphy),
HFD-340 (Vish)

3/5/98

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW**NDA:** 20-718**SUBMISSION DATE:** 04/01/96
06/14/96
11/13/96**INTEGRILIN™** (Intrifiban) Injection

Bolus vial (2 mg/mL, 10 mL), Infusion vial (0.75 mg/mL, 100 mL)

COR Therapeutics, Inc.

256 East Grand Avenue

South San Francisco, CA 94080

REVIEWER: Hae-Ryun Choi, Ph.D.**TYPE OF SUBMISSION:** NME**PRIORITY:** 1 S**I. SYNOPSIS:**

NDA 20-718 for **INTEGRILIN™**(intrifiban) for Injection was submitted by COR Therapeutics, Inc., on April 1, 1996. Integrilin Injection is intended for use as an adjunct with aspirin and heparin in patients undergoing percutaneous transluminal, coronary angioplasty (PTCA) for the prevention of acute cardiac ischemic complications (death, myocardial infarction, need for urgent intervention) related to abrupt closure of the treated coronary vessel. The proposed adult dosage of Integrilin Injection is an intravenous bolus of 135 $\mu\text{g}/\text{kg}$ administered immediately before the start of PTCA, followed by a continuous infusion of 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ for 20-24 hours.

Although the sponsors developed a multi point calibration curve assay method for quantifying Integrilin plasma concentrations and the sponsors attempted to cross validate selected samples previously analyzed with a single point calibrated assay, there are still the following outstanding deficiencies:

The pharmacokinetic parameter values must be judged in the light of this inadequate assay validation. Comparisons across time within a study can give some information. Comparisons across population lend doubt to the conclusions drawn. The main issue with this submission is the inadequate assay and how to judge conclusions drawn from the studies. Also one must keep in mind the presence of a PD surrogate marker used to evaluate some of the studies.

The pharmacokinetics of Integrilin were evaluated in five Phase I studies in 99 healthy normal volunteers, in 16 individuals in a renal impairment study (nine with moderate renal impairment and seven age-matched normal subjects), in four Phase II studies in 150 patients with ischemic heart disease and in a population pharmacokinetic substudy in 1725 patients undergoing coronary angiography in the IMPACT II (Phase III) study. However, the Integrilin assay was not adequately validated

for all of the above studies: Phase I (90-001, 91-002, 91-004, 91-006, 92-008 and 94-020), Phase II (91-007, 92-009, 93-012 and 93-015) and Phase III (93-014). Therefore, the pharmacokinetic data for Integrilin obtained from all these studies can give only qualitative information not quantitative information. Attached in Appendix II is the consult review by John Strong, Ph.D. (HFD-480) and the inspection report by Jacqueline O'Shaughnessy, Ph.D. (HFD-345) of analytical facility on 01/14-17/97.

Most administration regimens in these studies, including the IMPACT II study, have included an intravenous bolus followed by a continuous intravenous infusion for up to 72 hours. Bolus doses have ranged from 20 to 150 $\mu\text{g}/\text{kg}$ while infusion rates ranged from 0.2 to 1.5 $\mu\text{g}/\text{kg}\cdot\text{min}$.

No formal dose proportionality study was done. However, the C_{ss} and AUC values relative to the doses observed in studies 90-001/001A and 91-006 suggest that the pharmacokinetics of Integrilin are linear in the dosing range of 0.5 - 1.5 $\mu\text{g}/\text{kg}\cdot\text{min}$. Although the assay was inadequate, reasonable judgement of dose proportionality can be made within any of the two studies.

The estimated plasma half-life in four post-menopausal women (mean age 51.8 years) in study 92-008 was somewhat higher with a mean of 1.81 hours, and the estimate of plasma clearance was correspondingly lower with a mean of 157 mL/kg-hr as compared to those of healthy men. However, this can only be a hypothesis in view of the inadequate assay.

Study 94-020 was conducted in six subjects with moderate renal impairment (5F, 1M, mean age = 62.8 years, mean CrCl = 52.7 mL/min) who were otherwise healthy and seven age-matched subjects with normal renal function (1F, 6M, mean age = 56.7 years, mean CrCl = 81.5 mL/min). The subjects were given a bolus of 50 $\mu\text{g}/\text{kg}$ followed by a 24-hour infusion of 0.35 $\mu\text{g}/\text{kg}\cdot\text{min}$. There are no apparent differences in mean pharmacokinetic parameters between the really impaired and normal subjects, although the difference in estimated creatinine clearance was approximately 30 mL/min between the two groups. However, in view of the inadequate assay there is doubt cast upon conclusions drawn from comparisons across populations.

The pharmacokinetic parameters obtained from a definitive PK/PD study in patients undergoing coronary angioplasty (93-012) showed that in these patients overall estimate for total plasma clearance was lower with a mean of 142 mL/kg-hr and overall estimate for plasma half-life was higher with a mean of 2.21 hours than those observed in healthy young volunteers. However, numerical comparisons across populations are in doubt considering the inadequate assay.

Plasma Integrilin concentrations were determined in patients receiving a bolus and infusion of Integrilin to prevent thrombosis and associated ischemic complications following coronary angioplasty in a Phase III study (IMPACT II). Two Integrilin regimens were administered in this study, i.e., a 135 $\mu\text{g}/\text{kg}$ bolus followed by an infusion of 0.50 $\mu\text{g}/\text{kg}\cdot\text{min}$ or a 135 $\mu\text{g}/\text{kg}$ bolus followed by an infusion of 0.75 $\mu\text{g}/\text{kg}\cdot\text{min}$, with an intended infusion duration of 20-24 hours. One plasma sample for Integrilin concentration was obtained from each patient immediately prior to terminating the infusion whenever possible. A total of 1725 patients (median age 60 years, weight 84 kg and creatinine

clearance 71.6 mL/min), 888 at the high dose and 837 at the low dose, had an evaluable plasma sample and were evaluated in a population pharmacokinetic analysis. Integrilin plasma clearance was found to be proportional to the patient's weight, and estimated creatinine clearance, and inversely proportional to age. For every 10 mL/min that a patient's creatinine clearance differs from 71.6 mL/min, the clearance of Integrilin is predicted to change by about 4.6%, for every decade that a patient's age differs from 60 years, the clearance of Integrilin is predicted to change by about -5.3%, for every 10 kg that a patient's weight differs from 84 kg, the clearance of Integrilin is predicted to change by about 5.9%. No evidence for any pharmacokinetic interaction was detected. However, this can at best be a hypothesis which needs further support from studies using a validated assay.

Integrilin is eliminated, at least in part, by renal excretion. The primary degradation product found in human urine is deamidated Integrilin, a compound with about 41% the pharmacological activity of the parent compound (as assessed by *in vitro* inhibition of platelet aggregation). Deamidated Integrilin has been shown to be formed in urine *ex vivo*, and possibly within the bladder in man.

The mass balance of Integrilin was studied by estimating the renal excretion of the parent drug and its deamidated breakdown product in 23 patients undergoing coronary angioplasty in the IMPACT II study. Integrilin and deamidated Integrilin was quantitated in urine samples from patients, i.e., to determine the percentage of infused Integrilin that was excreted into urine. The total Integrilin recovered from all time points was compared to the total Integrilin administered to the patient to determine the percent recovery. Approximately 55% of the administered dose was excreted in the urine.

The metabolic pathways in human were not adequately characterized. However, the sponsors plan to conduct a radiolabeled drug metabolism study with Integrilin in normal volunteers using a sensitive and specific assay.

The average extent of Integrilin binding to human plasma protein was 24% at the concentration range of 0.05 - 15 $\mu\text{g/mL}$.

Integrilin increased the Simplate bleeding time approximately 2-fold when given alone or in conjunction with heparin. The combination of Integrilin and aspirin increased the Simplate bleeding time up to 5-fold, although this parameter was similarly increased in patients receiving aspirin alone.

Integrilin has a rapid onset of action and the effects on platelet aggregation and bleeding time are readily reversible upon discontinuation of the infusion. Bleeding times returned toward baseline within one hour after termination of infusion. Platelet aggregation returned rapidly toward baseline 2-4 hours after stopping infusion.

II. RECOMMENDATIONS:

NDA 20-718 submitted on April 1, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPEII). OCPB/DPEII has following comments and recommendations:

The medical officer(s) in HFD-180 should consider the above recommendations.

The Deficiencies and Labeling Comments on pages 20-22 should be forwarded to the sponsor.

02/21/97

Hae-Ryun Choi, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

ClinPharm/Biopharm Briefing on 02/11/97 (Drs. Malinowski, Strong, Huang, ML Chen, Hunt, Fleischer, Kaus, Choi).

RD initialed by Lydia Kaus, Ph.D., Team Leader _____
FT initialed by Lydia Kaus, Ph.D., Team Leader LK 2/21/97

cc: NDA 20-718, HFD-180, HFD-870 (ML.Chen, Hunt, Kaus, Choi), HFD-850 (Millison), HFD-340 (Viswanathan).

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Phase I Studies

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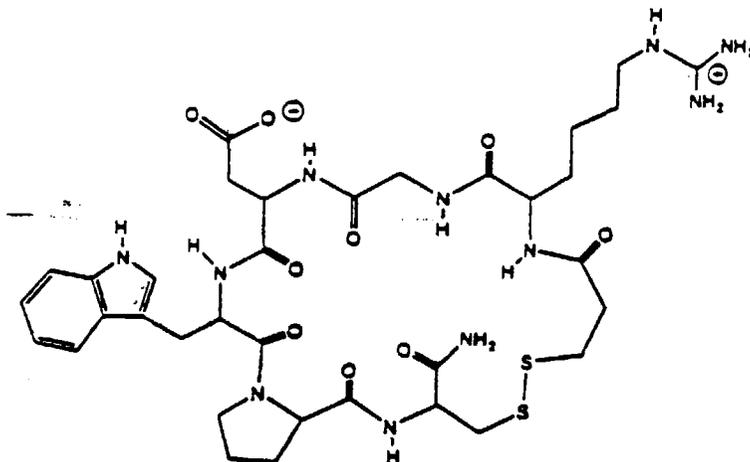
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III. BACKGROUND:

Integrilin™, a synthetic disulfide-linked cyclic heptapeptide, is known to reversibly inhibit platelet aggregation through specific binding to glycoprotein (GP) IIb/IIIa platelet receptor complex, thus blocking the binding of fibrinogen to the platelet surface. Integrilin is a cyclo (S-S)-mercaptopropronyl-(L) homoarginyl-glycyl-(L) aspartyl-(L) tryptophanyl-(L) prolyl-(L) cysteinamide, having a molecular weight of 832. The structural formula is:



The chiral amino acids are all in their natural L configurations.

Integrilin is an amorphous powder. It is insoluble in non-polar solvents such as hexane, but freely soluble in polar aqueous solvents and in highly polar organic solvents such as DMSO. Its stability decreases under basic conditions. The octanol/water partition coefficient is less than 0.01. It has two ionizable functional groups, the β -carboxyl group of the aspartic acid residue, with a pKa of 4.0, and the guanidino group of homoarginine, with an estimated pKa of > 12.5.

The pharmacokinetics of Integrilin were evaluated in five Phase I studies in 99 healthy normal volunteers, in 16 individuals in a renal impairment study (nine with moderate renal impairment and seven age-matched normal subjects), in four Phase II studies in 150 patients with ischemic heart disease and in a population pharmacokinetic substudy in 1725 patients undergoing coronary angiography in the IMPACT II study.

The Phase I studies were conducted to evaluate the safety and tolerability of a number of dosing regimens, and led to a decision to pursue an intravenous bolus administration followed by a continuous intravenous infusion. An initial Phase II study, the IMPACT study (92-009), a randomized, double-

blind, multicenter clinical trial, was conducted to evaluate the efficacy of Integrilin in a limited population of patients undergoing coronary angioplasty. A subsequent Phase II study, the IMPACT High-Low study (92-012), conducted in a limited population, was to assess the pharmacokinetics and pharmacodynamics of Integrilin following various dosing regimens in patients undergoing coronary angioplasty. A bolus dose of 135 $\mu\text{g}/\text{kg}$ was chosen for the IMPACT II study because it resulted in rapid inhibition of platelet aggregation to a mean of less than 20% of baseline values. A continuous infusion of 0.75 $\mu\text{g}/\text{kg}\text{-min}$ was chosen because it resulted in a similar mean inhibition of platelet aggregation at infusion information. The infusion rate of 0.5 $\mu\text{g}/\text{kg}\text{-min}$ was selected to ensure study of a safe regimen while maintaining efficacy. The IMPACT II study was a Phase III multicenter, double-blind, randomized, placebo-controlled study in 4010 patients undergoing coronary angioplasty. The study enrolled patients undergoing elective, urgent or emergency PTCA at 82 investigational centers in US.

IV. ANALYTICAL METHODOLOGY:

Plasma concentrations of Integrilin were determined at COR Therapeutics, Inc., South San Francisco, CA. Following the audit by the Division of Scientific Investigations of the Agency, it was concluded that the Integrilin assay was not adequately validated for all of the pharmacokinetic studies submitted

The audit report from Jacqueline A. O'Shaughnessy, Ph.D. (HFD-345) is attached in Appendix II. Also an independent review by John Strong, Ph.D. (HFD-480) of the submitted assay in the NDA is included in Appendix II.

V. DATA ANALYSIS:

A. Pharmacokinetics

Important pharmacokinetic variables are summarized using the following abbreviations:

AUC = Area under the plasma concentration-time curve
CL or CL_p = Total plasma clearance
CL_r = Renal clearance
C_{ss} = Plasma drug concentration at steady state
V_{ss} = Steady state volume of distribution
 τ = Infusion Time
T_{1/2} = Plasma half-life

In general, individual subject pharmacokinetic data from the Phase I and Phase II studies were fitted using a monoexponential (or single-compartment) approach. In one study (94-020), the pharmacokinetic data analysis in the three individuals from Part I of the study, was using the biexponential approach.

B. Pharmacodynamics

a. Bleeding Time:

Simplate bleeding time was measured in minutes and seconds. The following parameters were determined for each subject based on the visual inspection of the data:

BTmax = Maximum observed value of Simplate bleeding time after the start of the infusion expressed in minutes.

Tmax = The time associated with the observed BTmax

b. Platelet Aggregation:

The following parameters were determined for each subject based on visual inspection of data:

PAmin = Minimum value of platelet aggregation as a percent (%) of the baseline value

Tmin = Time of occurrence for PAmin

C. PK/PD Relationships:

In order to further define the PK/PD relationship, individual plasma Integrilin concentrations from each study were plotted vs. their corresponding platelet aggregation values (expressed as a percent of the pre-infusion baseline). If a relationship was established, then the concentration-response model was used to estimate the concentration which yields 50% inhibition of platelet aggregation (IC_{50}), and the concentration which yields 80% inhibition of platelet aggregation (IC_{80}).

VI. SUMMARY OF PHARMACOKINETIC/PHARMACODYNAMIC DATA:

A. Pharmacokinetics

a. Phase I Studies:

The mean pharmacokinetic parameters for Integrilin obtained from healthy volunteers are summarized in Table 1.

Table 1. A summary of mean pharmacokinetic parameters for Integrilin obtained from Phase I studies.

Study No.	Bolus Dose ($\mu\text{g}/\text{kg}$) and Infusion Rate ($-\text{g}/\text{kg}\text{-min}$)	Infusion Duration	Parameter					
			N	C _{ss} (ng/mL)	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	T _{1/2} (hr)
90-001/001A	0 & 0.2	90 min	4	44	61	307	320	0.64
	0 & 0.5	"	3	100	153	307	369	0.83
	0 & 1.0	"	3	210	325	278	282	0.67
	0 & 1.5	"	4	290	446	304	271	0.59
91-002/002X	0 & 0.5 + ASA	90 min	4	155	232	197	350	1.25
	0 & 0.5 + Hep.	"	4	134	202	236	336	1.02
	0 & 0.5 + ASA + Hep.	"	4	112	167	273	325	0.84
	0 & 1.0 + ASA	"	4	242	361	251	343	0.95
	0 & 1.0 + Hep.	"	4	209	328	309	431	1.04
	0 & 1.0 + ASA + Hep.	"	8	280	420	219	379	1.21
91-004	0 & 0.5	6 hr	4	120	747	248	449	1.25
	0 & 0.5 + ASA + Hep.	"	4	126	446	229	425	1.21
91-006	20 & 0.5 + Hep.	6 hr	4	138	992	203	438	1.53
	40 & 1.0 + Hep.	"	4	275	2050	204	512	1.72
92-008	90 & 1.0	90 min	4	213	1178	157	412	1.81

The four studies in healthy men (studies 90-001/001A, 91-002/002X, 91-004 and 91-006), all with a similar age distribution (range 19-44 years) yielded a range of group mean estimates for plasma clearance of 197-307 mL/kg-hr, for apparent volume of distribution of 271-512 mL/kg and for plasma half-life of 0.59-1.72 hours. However, reporting of these values in the labeling would be inappropriate in view of the inadequate assay.

Dose proportionality: No formal dose proportionality study was done. However, the C_{ss} and AUC values relative to the doses observed in studies 90-001/001A and 91-006 suggest that the pharmacokinetics of Integrilin in healthy subjects are linear in the dosing range of 0.5 - 1.5 $\mu\text{g}/\text{kg}\text{-min}$. Although the assay was inadequate, reasonable judgement of dose proportionality can be made within any of the two studies.

Menopause: The estimated plasma half-life in the four post-menopausal women (mean age 51.8 years) in study 92-008 was somewhat higher with a mean of 1.81 hours, and the estimate of plasma clearance was correspondingly lower with a mean of 157 mL/kg-hr as compared to healthy men. However, this can only be a hypothesis in view of the inadequate assay.

Renally impaired subjects: Study 94-020 was conducted in six subjects with moderate renal impairment (5F, 1M, mean age = 62.8 years, mean CrCl = 52.7 mL/min) who were otherwise healthy and seven age-matched subjects with normal renal function (1F, 6M, mean age = 56.7 years, mean CrCl = 81.5 mL/min). In a pilot phase of this study, another three individuals with a similarly impaired renal function were given a single intravenous Integrilin bolus of 70 µg/kg to obtain preliminary pharmacokinetic estimates as a guide to the dose selection of the second part of the study. In Part II, subjects were given a bolus of 50 µg/kg followed by a 24-hour infusion of 0.35 µg/kg-min. As shown in Table 2, there are no apparent differences in mean pharmacokinetic parameters between the really impaired and normal subjects, although the difference in estimated creatinine clearance was approximately 30 mL/min between the two groups. However, in view of the inadequate assay there is doubt cast on conclusions drawn from comparisons across populations.

Table 2. A summary of mean pharmacokinetic parameters for Integrilin obtained from Study 94-020

Study No.	Bolus Dose (µg/kg) and Infusion Rate (µg/kg-min)	Infusion Duration	Parameter					
			N	C _{ss} (ng/mL)	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	T _{1/2} (hr)
94-020	70		3	ND	1019	70	210	2.40
	50 & 0.35	24 hr	6	223	4505	81	ND	ND
7			272	5624	85	ND	ND	

ND = Not done.

b. Phase II Studies:

Table 3 summarizes the mean pharmacokinetic parameters of Integrilin after intravenous administration obtained from four Phase II studies.

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Table 3. A summary of mean pharmacokinetic parameters for Integrilin obtained from Phase II studies.

Study No.	Bolus Dose ($\mu\text{g}/\text{kg}$) and Infusion Rate ($\mu\text{g}/\text{kg}\cdot\text{min}$)	Infusion Duration	Parameter					
			N	C _{ss} (ng/mL)	AUC* (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	T _{1/2} (hr)
92-009	90 & 1.0 + ASA + Hep.	12 hr	7	299	ND	201	ND	ND
93-012	135 & 0.5 + ASA + Hep.	18-24 hr	16	254	--	124	413	2.43
	90 & 0.75 + ASA + Hep.	"	4	174	--	253	1046	3.34
	135 & 0.75 + ASA + Hep.	"	27	367	--	134	385	1.95
	180 & 1.0 + ASA + Hep.	"	4	458	--	150	517	1.96
91-007/007B	45 & 0.5 + ASA	24-72 hr	18	317	--	111	551	3.17
	90 & 1.0 + ASA	"	13	431	--	146	652	2.80
93-015	120 & 1.0	12-72 hr	7	675	--	102	358	2.46
	120 & 1.0 + Hep.	"	8	660	--	94	311	2.37
	135 & 1.0	"	5	633	--	108	393	2.46
	135 & 1.0 + Hep.	"	5	577	--	116	267	1.88
	150 + 1.25	"	6	1031	--	77	223	2.15
	150 & 1.25 + Hep.	"	6	795	--	104	228	1.78

* Due to the wide range of doses (i.e., infusion durations), the mean AUC is not representative and therefore not reported for several Phase II studies.

ND = Not done.

The two studies in patients undergoing coronary angioplasty included a pilot study in 24 patients (92-009) and a definitive PK/PD study in 52 patients (93-012). The few plasma samples obtained from 7 patients, all obtained at steady state, in the pilot study (92-009) permitted only an estimate of plasma clearance of 201 mL/kg-hr. However, this can only be a hypothesis in view of the inadequate assay.

The full characterization of the plasma concentration versus time profile was possible in most of 52 patients in the definitive study in this population of patients (93-012). The pharmacokinetic parameters obtained in this study included a lower overall estimate for total plasma clearance (142 mL/kg-hr) and a higher overall estimate for plasma half-life (2.21 hours) than those observed in healthy young volunteers. However, numerical comparisons across populations are in doubt considering the inadequate assay.

c. Phase III Study

Plasma Integrilin concentrations were determined in patients receiving a bolus and infusion of Integrilin to prevent thrombosis and associated ischemic complications following coronary angioplasty in a Phase III study (IMPACT II). Two Integrilin regimens were administered in this study, i.e., a 135 $\mu\text{g}/\text{kg}$ bolus followed by an infusion of 0.50 $\mu\text{g}/\text{kg}\text{-min}$ or a 135 $\mu\text{g}/\text{kg}$ bolus followed by an infusion of 0.75 $\mu\text{g}/\text{kg}\text{-min}$, with an intended infusion duration of 20-24 hours. One plasma sample for Integrilin concentration was obtained from each patient immediately prior to terminating the infusion whenever possible.

A total of 1725 patients, 888 at the high dose and 837 at the low dose, had an evaluable plasma sample and were evaluated in a population pharmacokinetic analysis. A summary of plasma concentrations obtained from this study is shown in Table 4.

Table 4. A summary of plasma Integrilin concentrations obtained from population pharmacokinetics analysis in IMPACT II, a Phase III study

Value	Low Dose (ng/mL)	High Dose (ng/mL)
N	888	837
Mean \pm SD	291 \pm 136	405 \pm 197
Median	275	391
Range		

Integrilin plasma clearance was found to be proportional to the patient's weight, and estimated creatinine clearance, and inversely proportional to age. The average patient in this study had an estimated Integrilin plasma clearance of 158 mL/min (median age 60 years, weight 84 kg and creatinine clearance 71.6 mL/min). For every 10 mL/min that a patient's creatinine clearance differs from 71.6 mL/min, the clearance of Integrilin is predicted to change by about 4.6%, for every decade that a patient's age differs from 60 years, the clearance of Integrilin is predicted to change by about -5.3%, for every 10 kg that a patient's weight differs from 84 kg, the clearance of Integrilin is predicted to change by about 5.9%. No evidence for any pharmacokinetic interaction was detected. However, conclusions from comparisons across populations are in doubt due to the inadequate assay.

B. Pharmacodynamics

a. Simplete Bleeding Time:

The mean maximum observed Simplete Bleeding times (BT_{max}) and the ratio of BT_{max}/Baseline BT obtained from Phase I and II studies are summarized in Table 5.

Table 5

A Summary of Mean Simplate Bleeding Times Obtained from Phase I Studies in Healthy Volunteers After Administration of Integrelin or Placebo Alone, with Aspirin (ASA) or Heparin, or Aspirin plus Heparin

Study No.	Bolus Dose (µg/kg) & Infusion Rate (µg/kg-min)	Infusion Duration	Treatment					
			Integrelin			Placebo		
			N	BT _{max} ^a	Ratio ^b	N	BT _{max}	Ratio
90-001/001A	0 & 0.2	90 min	5	7.08	1.18	2	5.00	1.08
	0 & 0.5	"	4	6.88	1.35	2	10.00	1.69
	0 & 1.0	"	4	10.15	1.85	2	6.75	1.12
	0 & 1.5	"	4	9.50	1.63	2	6.25	1.16
91-002/002X	0 & 0.5 + ASA	90 min	4	12.18	2.71	2	7.50	1.65
	0 & 0.5 + Heparin	"	4	6.45	1.20	2	7.50	1.35
	0 & 0.5 + ASA + Heparin	"	4	10.00	1.58	2	6.50	1.10
	0 & 1.0 + ASA	"	4	15.48	3.65	2	18.75	5.15
	0 & 1.0 + Heparin	"	4	11.00	2.13	2	6.00	1.56
	0 & 1.0 + ASA + Heparin	"	8	16.15	3.30	4	21.11	4.65
91-004	0 & 0.5	6 hr	6	9.00	2.04	2	5.75	1.55
	0 & 0.5 + ASA + Heparin	"	4	29.88	5.50	2	23.50	3.76
91-006	20 & 0.5 + Heparin	6 hr	4	8.50	2.60	2	4.25	1.05
	40 & 1.0 + Heparin	"	4	12.13	2.53	2	4.00	1.05
92-008	90 & 1.0	90 min	4	6.82	1.67	0	--	--
91-007	45 & 0.5 + ASA	24-72 hr	20	15.37	3.66			
	90 & 1.0 + ASA	"	19	19.55	3.62			
	ASA + Placebo + Heparin	"				22	16.13	2.56
92-009	90 & 1.0 + ASA + Heparin	4 hr	9	24.22	4.18			
	90 & 1.0 + ASA + Heparin	12 hr	9	16.22	2.74			
	Placebo + ASA + Heparin					7	10.50	1.14
93-012	90 & 0.75 + ASA + Heparin	18-24 hr	4	6.31	1.66			
	135 & 0.5 + ASA + Heparin	"	15	16.28	2.36			
	135 & 0.75 + ASA + Heparin	"	24	8.25	2.59			
	180 & 1.0 + ASA + Heparin	"	3	8.83	3.68			
	Placebo + ASA + Heparin	"				8	4.90	1.58
93-015	120 & 1.0	12-72 hrs	8	36.08	8.2			
	120 & 1.0 + Heparin	"	8	27.03	5.3			
	135 & 1.0	"	5	9.80	4.9			
	135 & 1.0 + Heparin	"	4	24.82	3.4			
	150 & 1.25	"	6	17.16	2.6			
	150 & 1.25 + Heparin	"	5	29.76	4.8			
	ASA + Placebo + Heparin	"				7	10.83	1.9

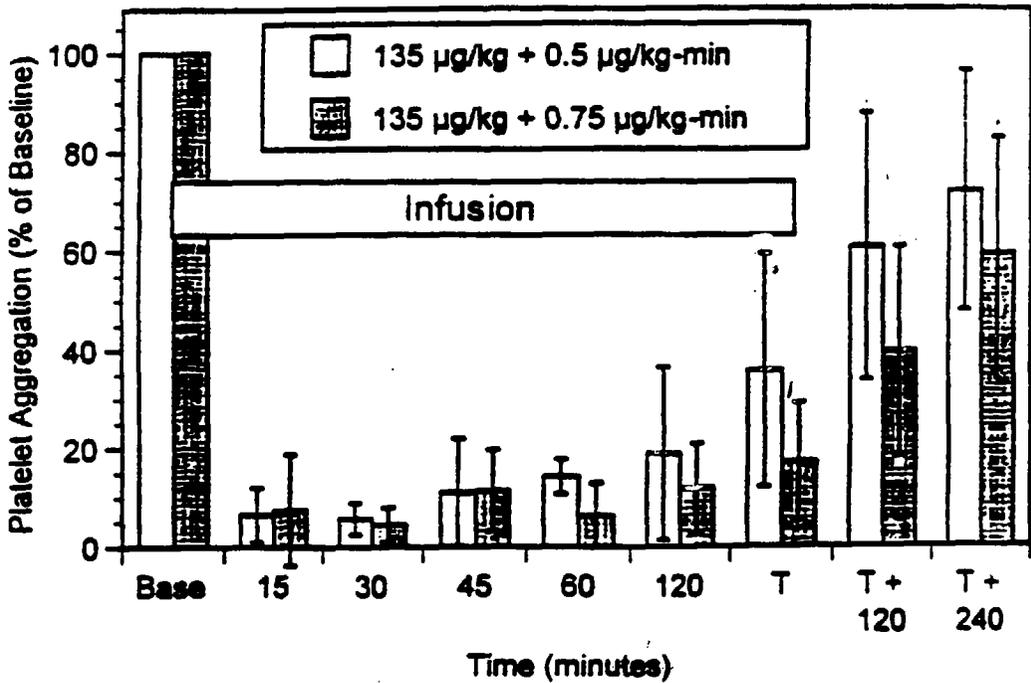
^a Maximum observed Simplate Bleeding Time expressed in minutes. For those subjects treated with Integrelin, the BT_{max} was the maximum observed BT value after the initiation of the infusion. For those subjects treated with Placebo, the BT_{max} was the maximum observed BT value after the baseline measurement.

^b The ratio of BT_{max} to Baseline BT.

Integrilin increased the Simplate bleeding time approximately 2-fold when given alone or in conjunction with heparin. The combination of Integrilin and aspirin increased the Simplate bleeding time up to 5-fold, although this parameter was similarly increased in patients receiving aspirin alone. Bleeding times are readily reversible upon discontinuation of the infusion.

b. Platelet Aggregation:

The effect of Integrilin on ADP-induced ex vivo platelet aggregation over time associated with the proposed dosing regimens, a 135 $\mu\text{g}/\text{kg}$ bolus followed by either a 0.5 or 0.75 $\mu\text{g}/\text{kg}\cdot\text{min}$ infusion, was studied in the definitive PK/PD study (93-012) and is shown in Figure 1. It was shown that the bolus produced a rapid and profound inhibition of aggregation. The infusion maintained a somewhat lesser degree of aggregation inhibition in a dose-dependent manner and with considerable overlap between the two infusion rates. Platelet aggregation returned rapidly toward baseline 2-4 hours after stopping a continuous infusion of 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$.



T=Termination (Median 20.8 hr for the 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ group and 20.4 hr for the 0.75 $\mu\text{g}/\text{kg}\cdot\text{min}$ group; Range 0.3-24.5 hr) T+120=Termination+120 min T+240=Termination+240 min

Figure 1: Ex Vivo Platelet Aggregation (mean \pm SD) Over Time in Patients Undergoing Coronary Angioplasty (Study 93-012)

The mean (\pm SD) platelet aggregation values (i.e., maximum inhibition) obtained from Phase I-II studies are summarized in Table 6. It appears that Integrilin causes a dose-dependent inhibition of platelet aggregation.

Table 6

A Summary of Mean (\pm SD) Platelet Aggregation Data for Integrilin Obtained from Phase I-II Studies

Study No.	Bolus Dose (μ g/kg) & Infusion Rate (μ g/kg-min)	Infusion Duration	Parameter	
			N	PA _{min} ^a
90-001/001A	0 & 0.2	90 min	5	27 \pm 26
	0 & 0.5	"	4	46 \pm 10
	0 & 1.0	"	4	9 \pm 3
	0 & 1.5	"	4	7 \pm 5
91-002/002X	0 & 0.5 + ASA	90 min	4	37 \pm 10
	0 & 0.5 + Heparin	"	4	47 \pm 12
	0 & 0.5 + ASA + Heparin	"	4	45 \pm 8
	0 & 1.0 + ASA	"	4	12 \pm 6
	0 & 1.0 + Heparin	"	3	25 \pm 16
	0 & 1.0 + ASA + Heparin	"	8	26 \pm 17
91-004	0 & 0.5	6 hr	4	8 \pm 6
	0 & 0.5 + ASA + Heparin	"	4	27 \pm 13
91-006	20 & 0.5 + Heparin	6 hr	4	8 \pm 9
	40 & 1.0 + Heparin	"	4	4 \pm 7
92-008	90 & 1.0	90 min	4	22
91-007/007B	45 & 0.5 + ASA	24-72 hr	16	34 \pm 18
	90 & 1.0 + ASA	"	15	25 \pm 19
92-009	90 & 1.0+ASA+Heparin	4 hr	10	10 \pm 7
	90 & 1.0+ASA+Heparin	12 hr	10	14 \pm 21
93-012	135 & 0.5 + ASA + Heparin	18-24 hr	14	6 \pm 6
	90 & 0.75 + ASA + Heparin	"	5	15 \pm 9
	135 & 0.75 + ASA + Heparin	"	25	4 \pm 4
	180 & 1.0 + ASA + Heparin	"	4	2 \pm 2
93-015	120 & 1.0	12-72 hr	8	7 \pm 9
	120 & 1.0 + Heparin	"	8	20 \pm 9
	135 & 1.0	"	5	10 \pm 6
	135 & 1.0 + Heparin	"	5	14 \pm 11
	150 & 1.25	"	6	5 \pm 6
	150 & 1.25 + Heparin	"	5	6 \pm 4
94-020	70	1-2 min	3	23 \pm 6
	50 & 0.35	24 hr	6 7	11 \pm 6 9 \pm 5

^a Minimum observed value of platelet aggregation, expressed as a percent (%) of baseline.

C. PK/PD Relationships

Individual plasma Integrilin concentrations from each study were plotted vs. their corresponding platelet aggregation values (expressed as a percent of the pre-infusion baseline). The concentration-response model was used to estimate the concentration which yields 50% inhibition of platelet aggregation (IC_{50}), and the concentration which yields 80% inhibition of platelet aggregation (IC_{80}).

The following Figure 2 showed the plasma concentration-platelet aggregation relationship obtained from the definitive pharmacokinetic study (93-012).

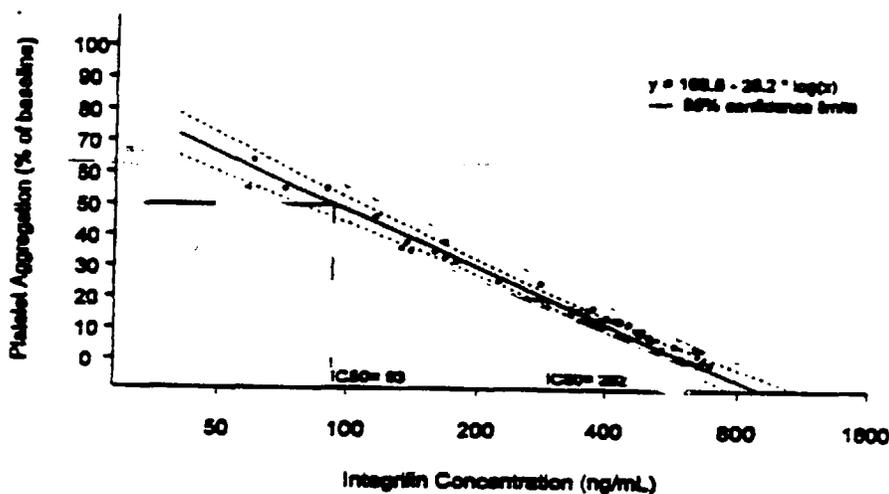


Figure 2: Plasma Concentration-Response Relationship for Integrilin in Patients Undergoing Coronary Angioplasty (Study 93-012)

The IC_{50} and IC_{80} for the ADP-induced ex vivo platelet aggregation by Integrilin obtained by regression analysis from Phase I-II studies are shown in Table 7.

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Table 7

A Summary of Mean Statistical Parameters Based on Regression Analysis from Phase I-II Studies

Parameter	Integrelin Alone			Integrelin + Aspirin	Integrelin + Heparin			Integrelin + Aspirin + Heparin	
	Study No.	Study No.	Study No.		Study No.	Study No.	Study No.	Study No.	Study No.
Study No.	90-001/001A 91-004	92-008 94-020	93-015	91-002/002X	91-002 91-006	93-015	91-007/007B	91-002/002X 91-004	93-012
Population	Healthy	Healthy	UA	Healthy	Healthy	UA	UA	Healthy	PTCA
Mean Age (yr) (Range)	27 19-42	57 45-65	64 52-84	33 21-44	28 20-40	66 47-86	60 39-79	30 22-43	58 34-76
N	13	7	18	8	15	18	25	16	46
Total Observ.	34	17	120	19	62	119	94	43	195
r ² (p-value)	0.59 (p<0.001)	0.81 (p<0.001)	0.40 (p<0.001)	0.63 (p<0.001)	0.60 (p<0.001)	0.44 (p<0.001)	0.27 (p<0.001)	0.40 (p<0.001)	0.56 (p<0.001)
Intercept (SE)	175 (22)	233 (24)	189 (17)	207 (33)	180 (16)	216 (19)	149 (17)	168 (25)	169 (9)
Slope (SE)	-32 (4.7)	-37 (4.6)	-26 (2.8)	-41 (7.6)	-32 (3.4)	-29 (3.1)	-18 (3.1)	-29 (5.6)	-26 (1.7)
IC ₅₀ (95% lim)	48 ^a (35 ^a , 59)	138 (117, 160)	200 (154, 241)	48 ^a (33-57)	59 (47 ^a , 69)	285 (238, 328)	232 (188, 289)	55 (40 ^a , 65)	93 (78, 107)
IC ₈₀ (95% lim)	123 (108, 145)	310 (258, 410 ^a)	630 (547, 750)	100 (88, 101)	152 (135, 174)	793 (682, 967)	1213 ^a (763, NA)	154 (127, 229 ^a)	292 (270, 316)

^a denotes an extrapolated value

Values for IC₅₀ varied accordingly and ranged from 48 to 59 ng/mL in young healthy subjects, from 117 to 143 ng/mL in post-menopausal women and patients with impaired renal function, and averaged 93 ng/mL in patients undergoing elective coronary angioplasty (study 93-012) and 285 ng/mL in patients with unstable angina (study 93-015).

The IC₈₀ ranged, on average, in healthy young subjects. In contrast, the results in the four post-menopausal women (mean age 52 years) and the three patients with renal impairment (mean age 64 years) ranged. These values are similar to the mean IC₈₀ (292 ng/mL) for patients undergoing elective angioplasty (study 93-012). However, comparisons across studies and populations are difficult in view of the inadequate assay.

VII. FORMULATIONS:

The marketed Integrilin Injection is supplied as a bolus injection vial (2.0 mg/mL, 10 mL) and an infusion vial (0.75 mg/mL, 100 mL) with the following quantitative composition:

	2.0 mg/mL	0.75 mg/mL
Component	(Quantity per mL)	(Quantity per mL)
Integrilin Drug Substance	2.0 mg*	0.75 mg*
Citric Acid, Monohydrate,		
Sodium Hydroxide, NF		
Water for Injection, USP		

The drug substance, Integrilin, was originally manufactured

Four lots of drug substance utilized in early toxicology and early Phase I and II studies were made using this solid phase synthesis process. In order to meet the commercial demands, a process was developed

It was stated that this process was much more amenable to scale-up, and in addition, it permitted peptide intermediates to be isolated and purified resulting in added control over the process.

VIII. Deficiencies:

The Integrilin assay was not adequately validated with respect to accuracy, precision, linearity, selectivity, and sensitivity. The following deficiencies should be forwarded to the firm:

IX. LABELING COMMENTS (to be sent to the firm):

1. The firm is recommended to replace the following proposed labeling (left-sided text) with right-sided text:

Pharmacokinetics

The pharmacokinetics of Integrilin are linear in the range of 0.5 to 1.5 $\mu\text{g}/\text{kg}\text{-min}$. In patients with coronary artery disease, the plasma elimination half-life is 2 to 3 hours, the plasma clearance is 100 to 150 $\text{mL}/\text{kg}\text{-hr}$ and the volume of distribution about 400 mL/kg . The extent of Integrilin binding to human plasma protein is about 25%.

For a 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion, steady-state plasma Integrilin concentrations are about 250 ng/mL and range from about 100 to 500 ng/mL .

The pharmacokinetics of Integrilin are linear in the range of 0.5 to 1.5 $\mu\text{g}/\text{kg}\text{-min}$. The extent of Integrilin binding to human plasma protein is about 25%.

For a 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion, steady-state Integrilin plasma levels are achieved rapidly

These plasma levels are achieved rapidly when the infusion is preceded by a 135 $\mu\text{g}/\text{kg}$ bolus.

In a 1725 patient population pharmacokinetic substudy within a large efficacy trial (IMPACT II), plasma clearance was proportional to the patient's weight and estimated creatinine clearance, and inversely proportional to age. The expected changes in steady-state plasma Integrilin concentrations are modest and correspond to an increase of about 20% from age 40 to 80, an increase of 4-5% for each 10 mL/min decrease in creatinine clearance, and a decrease of about 25% between 60 kg and 100 kg of body weight. Since these parameters have only modest effects on plasma Integrilin levels, no dose adjustment of the 135 $\mu\text{g}/\text{kg}$ bolus or the 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion are required for age, weight or renal function (up to a serum creatinine of 4.0 ng/dL).

Pharmacodynamics

INTEGRILINTM inhibits platelet aggregation in a dose- and concentration-dependent manner as demonstrated by ex vivo platelet aggregation using adenosine diphosphate (ADP) and other agonists to induce platelet aggregation.

The effect of an administered dose of INTEGRILINTM is observed within 15 minutes of the administration of a 135 $\mu\text{g}/\text{kg}$ intravenous bolus and is readily reversed 2-4 hours after stopping a continuous infusion of 0.5 $\mu\text{g}/\text{kg}\text{-min}$. Inhibition of ADP-induced ex vivo platelet aggregation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) showed a concentration-dependent effect with an IC_{50} (50% inhibitory concentration) of 93 ng/mL and IC_{80} (80% inhibitory concentration) of 292 ng/mL in citrated plasma.

when the infusion is preceded by a 135 $\mu\text{g}/\text{kg}$ bolus.

Inadequate assay validation precludes conclusions being made concerning special populations such as the elderly, females and those with renal failure.

OK

The effect of an administered dose of INTEGRILIN is observed within 15 minutes of the administration of a 135 $\mu\text{g}/\text{kg}$ intravenous bolus and is readily reversed 2-4 hours after stopping a continuous infusion of 0.5 $\mu\text{g}/\text{kg}\text{-min}$. Inhibition of ADP-induced ex vivo platelet aggregation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) showed a dose-dependent effect.

Administration of INTEGRILIN™ by intravenous bolus and infusion causes a slight (1.5 to 2-fold) increase in bleeding time which is rapidly reversible upon discontinuation of the infusion. While bleeding time in patients receiving aspirin is prolonged up to 5-fold, there is no incremental prolongation when INTEGRILIN™ is administered with aspirin. Concurrent administration of heparin does not contribute significantly to the prolongation of bleeding time caused by INTEGRILIN™ or aspirin. When administered alone, INTEGRILIN™ has no measurable effect on prothrombin time (PT) or activated partial thromboplastin time (aPTT). (See also PRECAUTIONS: Drug Interactions).

OK

Drug Interactions

In a population pharmacokinetic study performed within IMPACT II in 1725 patients, there was no evidence of a pharmacokinetic interaction between INTEGRILIN™ and the following coadministered drugs:

amlodipine	diazepam	fentanyl	metoprolol
atenolol	digoxin	furosemide	midazolam
atropine	diltiazem	heparin	morphine
captopril	diphenhydramine	lidocaine	nifedipine
cefazolin	enalapril	lisinopril	nitrites

Inadequate assay validation precludes conclusions being made concerning the drug interaction between INTEGRILIN™ and the following coadministered drugs:

amlodipine	diazepam	fentanyl	metoprolol
atenolol	digoxin	furosemide	midazolam
atropine	diltiazem	heparin	morphine
captopril	diphenhydramine	lidocaine	nifedipine
cefazolin	enalapril	lisinopril	nitrites

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APPENDIX I

Individual Study Summaries

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Study 90-001/90-001A

Title: A double-blind, randomized, placebo-controlled safety evaluation of escalating doses of Integrilin administered as a continuous IV infusion for 90 minutes.

Study Dates: 4/25/91 - 11/13/91

Objectives:

- To assess the safety of selected doses of Integrilin administered by continuous IV infusion over 90 minutes.
- To determine the lowest dose of Integrilin that completely inhibits platelet function as assessed by *ex vivo* studies of platelet aggregation but that does not prolong bleeding time; to determine the dose of Integrilin that prolongs the bleeding time to twice the normal (8-12 min in study 90-001 and 14 min in study 90-001A); to assess the dose response observed at lower dose levels; and to determine a no-effect dose.
- To evaluate the pharmacokinetics of Integrilin and the relationship between plasma concentrations of Integrilin and inhibition of platelet function, as measured by platelet aggregometry and bleeding time.

Study Design: Studies 90-001 and 90-001A were double-blind, randomized, placebo-controlled trials, and were conducted at the same research facility. In study 90-001, Integrilin doses of 0.2 and 0.5 $\mu\text{g}/\text{kg}\text{-min}$ were administered, and in study 90-001A, doses of 1.0 and 1.5 $\mu\text{g}/\text{kg}\text{-min}$ were given. A total of 25 healthy men with a mean age of 26.6 years (range 19-42) were enrolled. Of these, 24 subjects were divided into four groups of 6 subjects each and were randomly assigned in a 2:1 ratio to receive 90-minute intravenous infusions of 0.2, 0.5, 1.0, or 1.5 $\mu\text{g}/\text{kg}\text{-min}$ of Integrilin or matching placebo. Infusions were administered in a progressive rising-dose fashion. An additional single volunteer was administered Integrilin 0.2 $\mu\text{g}/\text{kg}\text{-min}$ for 90 minutes in a nonrandomized, open-label fashion at the beginning of the study to familiarize the investigator's staff with the study procedures.

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: Batch/Lot# A0004A
- Placebo, Batch/Lot# A0005A

PK/PD Sampling Times:

- Plasma samples for Integrilin assay: 60 minutes pre-infusion, 30, 60, 90 minutes after the start of the infusion and 1, 3, 5, 7, 10, 15, and 30 minutes after the end of the infusion.
- Pharmacodynamics: Platelet aggregation & bleeding time

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: 1 subject missing screening CBC
90-minute urinalysis data collected for only one subject

Results:

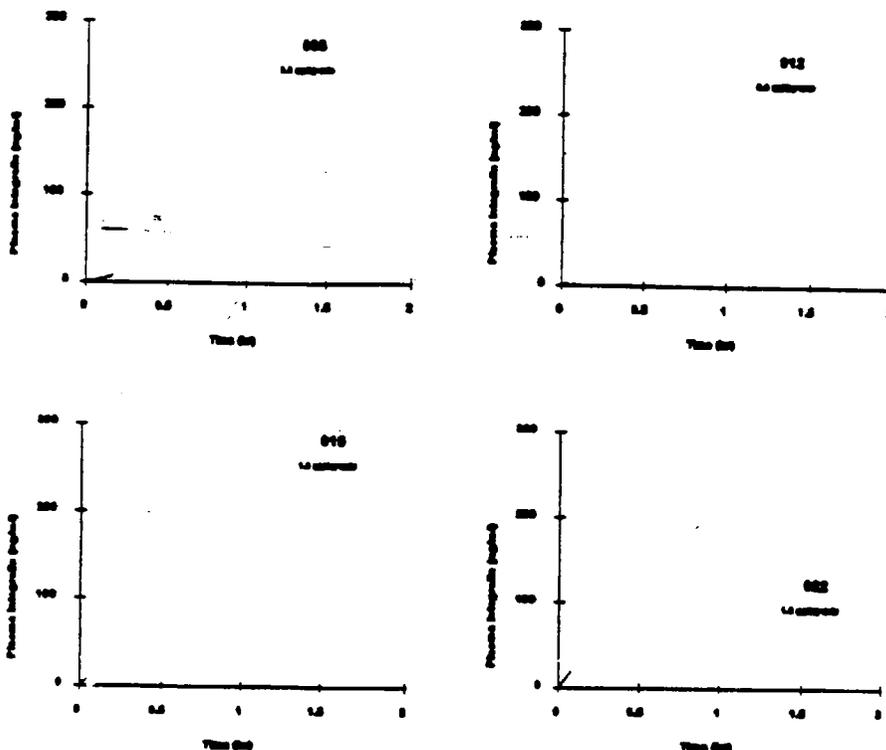
Pharmacokinetics:

Integrilin plasma concentration: The pharmacokinetic parameters for Integrilin of each dose group are summarized in the table below:

Infusion Rate ($\mu\text{g}/\text{kg}\text{-min}$)	AUC ($\text{ng}\text{-hr}/\text{mL}$)	CL ($\text{mL}/\text{kg}\text{-hr}$)	Vss (mL/kg)	Css (ng/mL)	T1/2 (hr)
0.2 Mean Range N	61 4	307 4	320 4	44.0 4	0.64 4
0.5 Mean Range N	153 3	307 3	369 3	100 3	0.83 3
1.0 Mean Range N	325 3	278 3	282 3	210 3	0.67 3
1.5 Mean Range N	446 4	304 4	271 4	290 4	0.59 4

At the 0.2 $\mu\text{g}/\text{kg}\text{-min}$ infusion rate, since all of the plasma Integrilin levels were at or below the LOQ, the reported pharmacokinetic parameters are unreliable. However, those are presented here only for the sake of completeness. At the 0.5 $\mu\text{g}/\text{kg}\text{-min}$ and higher infusion rates, nearly all of the plasma Integrilin concentrations were above the LOQ.

Selected plasma concentration versus time plots are presented below for four subjects, one from each dose group.



Legend: The experimental plasma concentration of Integrilin over time is shown as the symbols and solid curve is estimated from the best fit function.

The duration of the infusion was not sufficient to reach steady-state and the collection of blood for Integrilin assay was too short relative to the apparent elimination $T_{1/2}$. Thus the estimated mean $T_{1/2}$ of 41 minutes for the 14 subjects is less precise and likely an underestimate.

The estimated mean values of C_{ss} were 44 ng/mL, 100 ng/mL, 210 ng/mL, 290 ng/mL for the four increasing infusion rates, respectively.

The mean AUC's normalized to a unit dose of 1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$ are similar for the four dose groups.

The mean apparent volume of distribution values ranged
clearance values ranged

The mean plasma

Pharmacodynamics:

a. Simplate Bleeding Time: The following is a summary of the mean effect on bleeding time for each of the Integrilin infusion groups and placebo expressed as maximum change from baseline (as a ratio of the baseline value).

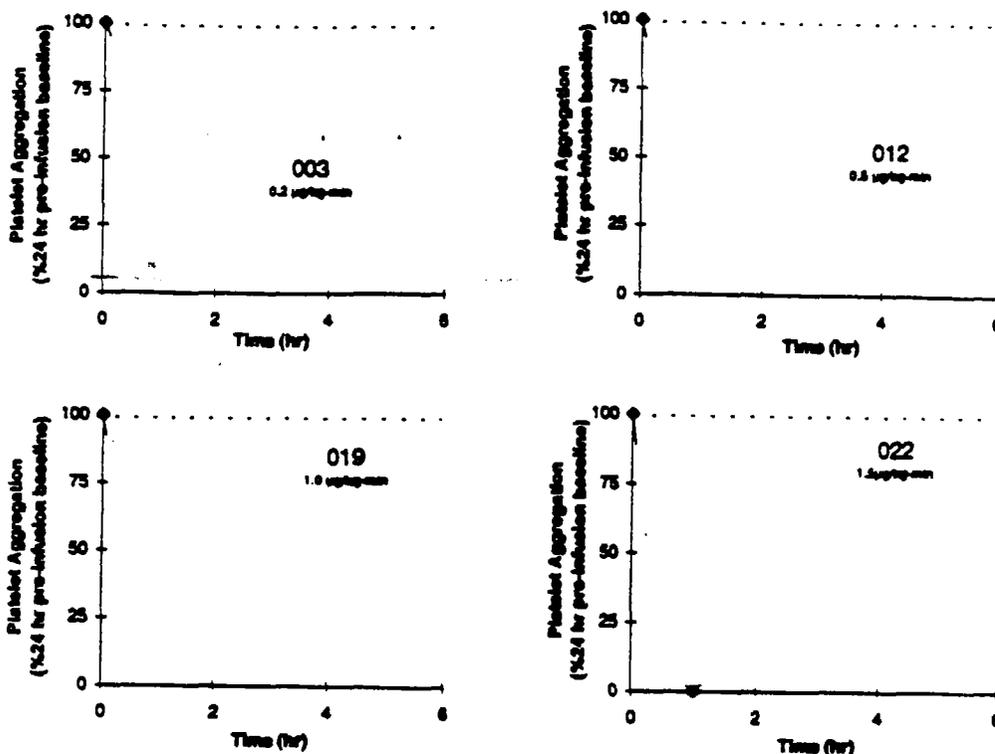
	Placebo	0.2 $\mu\text{g}/\text{kg}\text{-min}$	0.5 $\mu\text{g}/\text{kg}\text{-min}$	1.0 $\mu\text{g}/\text{kg}\text{-min}$	1.5 $\mu\text{g}/\text{kg}\text{-min}$
N	8	5	4	4	4
Mean	1.25	1.18	1.35	1.85	1.63
S.D.	0.32	0.43	0.17	0.47	0.30
Range					

b. Platelet Aggregation: The following is the mean effect on platelet aggregation for each Integrilin infusion dose and placebo expressed as maximum change from baseline for the 10 μM ADP results.

	Placebo	0.2 $\mu\text{g}/\text{kg}\text{-min}$	0.5 $\mu\text{g}/\text{kg}\text{-min}$	1.0 $\mu\text{g}/\text{kg}\text{-min}$	1.5 $\mu\text{g}/\text{kg}\text{-min}$
N	8	5	4	4	4
Mean (%)	80.9	27.0	46.0	9.3	6.5
S.D.	14.8	25.6	10.1	3.2	5.2
Range					

After the Integrilin infusion began, the extent of platelet aggregation reached minimum mean values relative to baseline of 27% and 46% for the two lower infusion rates and 9.3% and 6.5% for the two highest infusion rates, respectively, at 10 μM ADP. The times of these maximums occurred at 60-124 minutes for the three lower infusion rates and at 69 minutes for the 1.5 $\mu\text{g}/\text{kg}\text{-min}$ group.

Selected results for platelet aggregation over time are presented below for four subjects, one from each dose group is shown in the following figure.



Legend: Platelet aggregation (ADP 10 µM) as a percent of 24 hr pre-infusion baseline. Symbols are experimental values and lines connect the data points. The dotted line indicates 100% (baseline value).

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

a. Pharmacokinetics: Based on the C_{ss} and AUC values obtained, the pharmacokinetics of Integrilin appear to be linear and dose-proportional between the doses of 0.2 µg/kg-min and 1.5 µg/kg-min. Although the assay was inadequate, reasonable judgement of dose proportionality can be made with this study.

b. Pharmacodynamics: Integrilin alone, administered as a continuous 90 minute intravenous infusion, appears to produce a dose-dependent inhibition of ex vivo platelet aggregation. Infusion rates of 1.0 and 1.5 $\mu\text{g}/\text{kg}\text{-min}$ resulted in $>90\%$ inhibition of ex vivo platelet aggregation. At infusion rates that produce $>90\%$ inhibition ex vivo platelet aggregation, there was a negligible to slight increase in bleeding time. Bleeding times normalized within 15 to 30 minutes following cessation of infusion; platelet aggregation normalizes within two to four hours depending on the extent of inhibition.

**APPEARS THIS WAY
ON ORIGINAL**

Study 91-002/002X

Title: A double-blind, randomized, placebo-controlled safety evaluation of Integrilin administered as a continuous IV infusion for 90 minutes in combination with aspirin or heparin, or aspirin plus heparin.

Study Dates: 8/26/91 - 12/26/91

Objectives:

- To assess the safety of selected doses of Integrilin administered by continuous IV infusion at an infusion rate of 0.5 or 1.0 $\mu\text{g}/\text{kg}\text{-min}$ over 90 minutes in subjects who received aspirin, heparin, or aspirin plus heparin.
- To evaluate the PK/PD of Integrilin in combination with aspirin, heparin, or aspirin plus heparin.

Study Design: This was a double-blind, randomized, single-center, placebo-controlled study in normal healthy male volunteers. Forty-two healthy men with a mean age of 28.6 years (range 21-44) were enrolled and completed the study. Integrilin 0.5 or 1.0 $\mu\text{g}/\text{kg}\text{-min}$ or matching placebo was infused intravenously for 90 minutes. Aspirin was administered as a 162-mg oral dose twice, 12 hours and 1-2 hours before infusion of Integrilin; heparin was administered as an intravenous bolus of 5000 units 12 hours before Integrilin followed by a 1000 units/hour infusion until completion of Integrilin administration (a total of 13.5 hours). Eighteen subjects received 0.5 $\mu\text{g}/\text{kg}\text{-min}$ (or placebo) plus aspirin (6 subjects), heparin (6 subjects), or aspirin and heparin (6 subjects); 24 subjects received 1.0 $\mu\text{g}/\text{kg}\text{-min}$ (or placebo) plus aspirin (6 subjects), heparin (6 subjects), or aspirin and heparin (12 subjects). Within each subgroup, subjects were assigned Integrilin or placebo in a ratio of 2:1 as follows:

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Group	Number of Subjects	Treatment
1	4 2	Integrilin 0.5 μ g/kg-min + Aspirin Placebo + Aspirin
2	4 2	Integrilin 0.5 μ g/kg-min + Heparin Placebo + Heparin
3	4 2	Integrilin 0.5 μ g/kg-min + Aspirin + Heparin Placebo + Aspirin + Heparin
4	4 2	Integrilin 1.0 μ g/kg-min + Aspirin Placebo + Aspirin
5	4 2	Integrilin 1.0 μ g/kg-min + Heparin Placebo + Heparin
6	8 4	Integrilin 1.0 μ g/kg-min + Aspirin + Heparin Placebo + Aspirin + Heparin

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: Batch/Lot# A0004A
- Placebo, Batch/Lot# A0005A
- Bayer® Children's Chewable Aspirin, 162 mg.
- Heparin Sodium Injection, USP,
- LyphoMed® Heparin Sodium Injection, USP,

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 30, 60, 90 minutes during infusion; 3, 7, 10, 15, 30 and 60 minutes, and 2 and 4 hours during post-infusion (subjects 1-15). 10, 30, and 60 minutes and 2, 4 and 6 hours post-infusion (subjects 16-42).

Pharmacodynamics: Platelet aggregation & Simplate bleeding time

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: unscheduled CBC (60 minutes post-infusion) - 42
eligibility violations - 3
heparin administration violations - 5

Results:

Pharmacokinetics:

Integrilin plasma concentration: The mean (\pm SD) Integrilin pharmacokinetic parameters for Integrilin based on one-compartmental analysis are summarized in the table below:

Bolus Dose (μ g/kg) and Infusion Rate (μ g/kg-min)	Infusion Duration	N	C _{ss} (ng/mL)	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	T _{1/2} (hr)
0 + 0.5 + ASA	90 min	4	155 \pm 22	232 \pm 33	197 \pm 27	350 \pm 11	1.25 \pm 0.16
0 & 0.5 + Hep.	"	4	134 \pm 38	202 \pm 57	236 \pm 59	336 \pm 68	1.02 \pm 0.21
0 & 0.5 + ASA + Hep.	"	4	112 \pm 17	167 \pm 25	273 \pm 48	325 \pm 49	0.84 \pm 0.16
0 & 1.0 + ASA	"	4	242 \pm 28	361 \pm 40	251 \pm 28	343 \pm 48	0.95 \pm 0.11
0 & 1.0 + Hep.	"	4	209 \pm 57	328 \pm 91	309 \pm 108	431 \pm 24	1.04 \pm 0.27
0 & 1.0 + ASA + Hep.	"	8	280 \pm 44	420 \pm 66	219 \pm 34	379 \pm 66	1.21 \pm 0.17

The mean terminal plasma half-life range for Integrilin was _____ hours. The mean plasma clearance values ranged _____. Dose-dependent parameters such as AUC and the estimated C_{ss} appear to increase in a dose-related manner. The pharmacokinetics of a 0.5 μ g/kg-min or 1.0 μ g/kg-min Integrilin infusion in healthy subjects appear to be independent of treatment with aspirin, heparin or the combination of aspirin and heparin.

Pharmacodynamics:

a. Simple Bleeding Time: The following is a summary of the mean effect on bleeding time expressed as maximum change from baseline (as a ratio of the baseline value).

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Simplite Bleeding Time
Maximum Change from Baseline as a Ratio of Baseline

Placebo Infusion			
	Aspirin	Heparin	Aspirin + Heparin
N	4	4	8
MEAN	3.40	1.45	3.47
S.D.	2.48	0.40	3.06
Range			

Integrelin 0.5 µg/kg-min			
	Aspirin	Heparin	Aspirin + Heparin
N	4	4	4
MEAN	2.71	1.20	1.58
S.D.	2.43	0.12	0.49
Range			

Integrelin 1.0µg/kg-min			
	Aspirin	Heparin	Aspirin + Heparin
N	4	4	8
MEAN	3.65	2.13	3.30
S.D.	1.78	0.78	1.62
Range			

Aspirin had a significant though highly variable effect on bleeding time whether given alone, in combination with heparin, Integrilin or both. The overall mean effect of aspirin resulted in an increased bleeding time of approximately 3-fold relative to baseline determinations. Heparin had little effect on bleeding time as did the 0.5 $\mu\text{g}/\text{kg}\text{-min}$ dose of Integrilin. At the higher dose of 1.0 $\mu\text{g}/\text{kg}\text{-min}$ Integrilin appears to produce a small increase in bleeding time but this was largely masked in the presence of aspirin by the effect of aspirin itself.

b. Platelet Aggregation: The following is the mean effect on platelet aggregation expressed as maximum change from baseline for the 10 μM ADP results.

**APPEARS THIS WAY
ON ORIGINAL**

**Platelet Aggregation (10 μ M ADP)
Maximum Change from Baseline as a Percent of Baseline**

Placebo Infusion			
	Aspirin	Heparin	Aspirin + Heparin
N	3	4	6
MEAN*	96	91	82
S.D.	32	17	13
Range			
* (% change from baseline)			

** Data from one subject (#035) with a PA_{max} of 14% were not included in the mean

Integrelin 0.5 μg/kg-min			
	Aspirin	Heparin	Aspirin + Heparin
N	4	4	4
MEAN*	37	47	45
S.D.	9.8	12	7.8
Range			
* (% change from baseline)			

Integrelin 1.0 μg/kg-min			
	Aspirin	Heparin	Aspirin + Heparin
N	4	3	6
MEAN	12	25	26
S.D.	6.0	16	17
Range			
* (% changer from baseline)			

Neither aspirin nor heparin, when administered individually or in combination, had a significant effect on platelet aggregation induced by 10 μ M ADP. Integrilin appears to have a dose related effect producing a decrease in platelet aggregation to 42.8% of baseline at the 0.5 μ g/kg-min dose and 21.9% of baseline at the 1.0 μ g/kg-min dose. There was no evidence of an interaction of Integrilin with aspirin heparin, or both in the effect on ex vivo platelet aggregation.

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combing data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

Pharmacokinetics: The mean terminal plasma half-life range for Integrilin was between 0.84 and 1.25 hours. The mean plasma clearance values ranged Dose-dependent parameters such as AUC and the estimated C_{ss} appear to increase in a dose-related manner. The pharmacokinetics of a 0.5 μ g/kg-min or 1.0 μ g/kg-min Integrilin infusion in healthy subjects appear to be independent of treatment with aspirin, heparin or the combination of aspirin and heparin. However, this can only be a hypothesis in view of the inadequate assay.

Pharmacodynamics: Neither aspirin, heparin nor the combination of the two were found to influence the degree of Integrilin-induced ex vivo platelet aggregation inhibition. Integrilin appears to have a dose related effect producing a decrease in platelet aggregation.

Aspirin had a significant though highly variable effect on bleeding time whether given alone, in combination with heparin, Integrilin or both. The overall mean effect of aspirin resulted in an increased bleeding time of approximately 3-fold relative to baseline determinations. Heparin had little effect on bleeding time as did the 0.5 μ g/kg-min dose of Integrilin. At the higher dose of 1.0 μ g/kg-min Integrilin appears to produce a small increase in bleeding time but this was largely masked in the presence of aspirin by the effect of aspirin itself.

**APPEARS THIS WAY
ON ORIGINAL**

Study 91-004

Title: A double-blind, randomized, placebo-controlled safety evaluation of Integrilin administered as a continuous IV infusion for six hours alone and in combination with aspirin plus heparin.

Objectives:

- To assess the safety of Integrilin administered by continuous IV infusion at an infusion rate of 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ over 6 hours.
- To evaluate the PK/PD of Integrilin alone and in combination with aspirin plus heparin.

Study Dates: 10/21/91 - 7/8/92

Study Design: This was a single-center, double-blind, randomized, placebo-controlled study in healthy adult men. Fifteen healthy men entered the study, 14 were randomized and one subject was discontinued prior to randomization due to an excessive bleeding time at baseline. Subjects who completed the study had a mean age of 28.2 years (range 20-40). There were 10 Integrilin-treated subjects with a mean age 28.9 years (range 20-40) and 4 placebo-treated subjects with a mean age 26.5 years (range 23-29).

The ratio of subjects receiving Integrilin to those receiving placebo was 2:1. A total of 12 subjects completed the study, six (four Integrilin, two placebo) in each of two groups: A and B. Subjects in Groups A and B each received Integrilin 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ or matching placebo by IV infusion for six hours. However, subjects in Group B additionally received (1) 162 mg of aspirin 12 hours before and again at 2 hours before infusion of study drug and (2) a bolus of 5000 units of heparin 12 hours before infusion immediately followed by a heparin infusion of 1000 units per hour until completion of study drug administration. Group A was studied prior to Group B.

	Infusion Rate	Duration	Co-Administered Drugs
Group A	0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$	6 hours	None
Group B	0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$	6 hours	Aspirin + Heparin

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: Batch/Lot# A0004A
- Placebo, Batch/Lot# A0005A
- Bayer® Children's Chewable Aspirin, 162 mg,
- Heparin Sodium Injection, USP,
- LyphoMed® Heparin Sodium Injection, USP,

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 60 minutes pre-infusion; 30, 60, and 90 minutes and 2, 4, and 6 hours during infusion; 5, 10, 30, and 60 minutes and 2, 4, and 6 hours post-infusion.

Urine samples for Integrilin assay: Urine was collected from five of the volunteers during and after Integrilin infusion. Collection intervals were: 0-1, 1-2, 2-4, 4-6 hours during infusion, 0-6, 6-24 hours post-infusion.

Pharmacodynamics: Platelet aggregation and Simplate bleeding time

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: eligibility violations - 1
 early termination of infusion - 1
 heparin administration violations - 2

RESULTS

Pharmacokinetics:

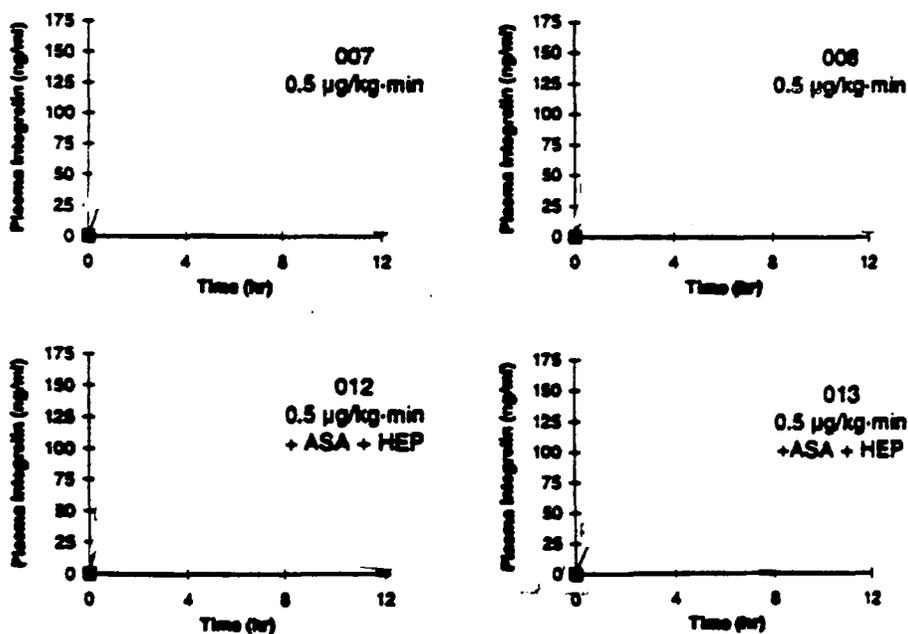
a. Integrilin plasma concentration: The pharmacokinetic parameters for Integrilin are summarized in the following table:

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ON ORIGINAL**

Treatment	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	C _{ss} (ng/mL)	T _{1/2} (hr)
<u>Group A: Integrilin Alone</u> Mean ± SD Range N	747 ± 149 /	248 ± 61	449 ± 6	120 ± 29	1.25 ± 0.35
<u>Group B: Integrilin + Aspirin + Heparin</u> Mean ± SD Range N	446 ± 380	229 ± 52	425 ± 79	126 ± 30	1.21 ± 0.13

The mean plasma elimination half-life was approximately 1.2 hours. The mean values for plasma clearance of Integrilin were similar in the two groups with and without aspirin plus heparin (248 mL/kg-hr vs. 229 mL/kg-hr) as was the volume of distribution (449 mL/kg vs. 425 mL/kg).

Selected plasma Integrilin concentration versus time plots for four subjects are presented below.



Legend: The experimental plasma concentration of Integrilin over time is shown as the symbols and solid curve is estimated from the best fit function.

b. Integrilin Urine Concentration: Urine volume measurements for the first collection sample were not recorded for two subjects. An estimate of the total amount of Integrilin and its deamidation product excreted during and for 24 hours after the infusion was available from only three subjects and the following are the results:

Subject No.	Amount (μg)	Recovery (%)
004		
007		
008		

Pharmacodynamics:

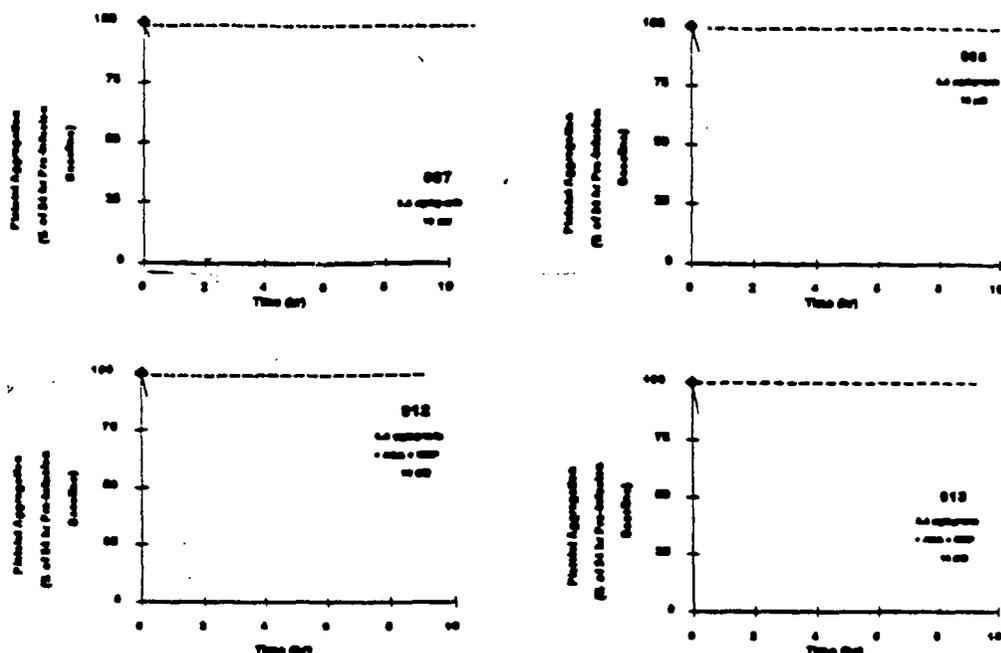
a. Simplate Bleeding Time: The following is a summary of the mean effect on bleeding time for each of the Integrilin infusion groups and placebo expressed as maximum change from baseline (as a ratio of the baseline value).

	Integrilin alone	Integrilin +ASA +Hep	Placebo +ASA +Hep	Placebo alone
N	6	4	2	2
Mean	2.04	5.50	3.80	1.55
S.D.	0.70	3.03	0	0.05
Range				

b. Platelet Aggregation: The following is the mean effect on platelet aggregation for each Integrilin infusion dose and placebo expressed as maximum change from baseline for the 10 μM ADP results.

	Integrilin alone	Integrilin +ASA +Hep	Placebo +ASA +Hep	Placebo alone
N	4	4	2	1
Mean	8	27	74	61
S.D.	6	13	4	
Range				

Selected platelet aggregation over time plots for four subjects are shown in the following figure.



Legend: Platelet aggregation (ADP 10 μ M) as a percent of 24 hr pre-infusion baseline. Symbols are experimental values and lines connect the data points. The dotted line indicates 100% (baseline value).

When administered as a continuous six-hour infusion, Integrilin alone at 0.5 μ g/kg-min produced a time-dependent inhibition of ex vivo platelet aggregation. At four to six hours of infusion, 0.5 μ g/kg-min of Integrilin produced >90% inhibition of ex vivo platelet aggregation with a minimum increase in bleeding time. Normalization of bleeding time and platelet function following cessation of the six-hour infusion were similar to that observed following a 90-minute infusion.

When administered together with aspirin plus heparin, Integrilin at 0.5 μ g/kg-min produced >70% inhibition of ex vivo platelet aggregation and caused increased bleeding times of >30 minutes in three of four subjects as early as 1 hour into the infusion. Placebo was also associated with a bleeding

time of 30 minutes in one subject, and 17 minutes in the second subject. One subject received a full six hours of Integrilin infusion without any corresponding change of bleeding time from the 75-minute pre-infusion baseline (13.5 minutes). Similarly, one of the two subjects received a full six hours of placebo infusion without further increase in bleeding time. Subjects who developed bleeding times of > 30 minutes had their infusion of Integrilin plus heparin (or placebo plus heparin) terminated immediately upon observation of the extended bleeding time. Normalization of bleeding times occurred within 60-90 minutes of cessation of the infusion. The increased bleeding times obtained in this study is believed to be attributable primarily to aspirin administration.

The study drug infusion was discontinued prematurely in 3 of 4 subjects administered Integrilin plus aspirin and heparin and in 1 of 2 subjects administered placebo plus aspirin and heparin because of abnormal bleeding indices.

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

Pharmacokinetics:

- The pharmacokinetics of Integrilin appear to be unchanged in the presence of aspirin and heparin.
- The percent of administered dose of Integrilin recovered in the urine during and for 24 hours after the infusion as Integrilin and its deamidation product in three subjects ranged

Pharmacodynamics:

- The combination of aspirin and heparin, with Integrilin or placebo, was associated with profound effects on Simplate bleeding time in some of the subjects in this study. Integrilin alone, at a dose of 0.5 $\mu\text{g}/\text{kg}\text{-min}$ administered up to 6 hours, did not appear to have a significant effect on bleeding time compared to placebo.
- Integrilin infusion at a dose of 0.5 $\mu\text{g}/\text{kg}\text{-min}$ for six hours resulted in near complete inhibition of ex vivo platelet aggregation.

Study 91-006/006X

Title: A double-blind, randomized, placebo-controlled safety evaluation of Integrilin administered as an intravenous bolus dose and six-hour continuous infusion in combination with heparin.

Study Dates: 1/9/92 - 2/17/92

Objectives:

- To assess the safety of Integrilin administered by IV bolus of 20 or 40 $\mu\text{g}/\text{kg}$ followed by continuous IV infusion at an infusion rate of 0.5 or 1.0 $\mu\text{g}/\text{kg}\text{-min}$ over 6 hours. Safety was assessed with Integrilin in combination with heparin.
- To evaluate the PK/PD of Integrilin in combination with heparin.

Study Design: This was a single-center, double-blind, randomized, placebo-controlled study in healthy adult men. Fourteen healthy men with a mean age of 25.4 years (range 20-34) were enrolled in the study. Twelve subjects (8 Integrilin, 4 placebo) were randomized and completed the study and were included in the pharmacokinetic and pharmacodynamic analysis. Subjects were enrolled in two groups: A and B. Each group of subjects received Integrilin 20 or 40 $\mu\text{g}/\text{kg}$ bolus and an infusion of Integrilin 0.5 or 1.0 $\mu\text{g}/\text{kg}\text{-min}$ or matching placebo by IV infusion for six hours. Twelve hours before the study drug administration all subjects received a bolus of 5,000 units of heparin, and a heparin infusion of 1,000 units per hour until completion of study drug administration. Group A was studied prior to Group B.

	Bolus	Infusion Rate	Duration	Co-Administered Drugs
Group A	20 $\mu\text{g}/\text{kg}$	0.5 $\mu\text{g}/\text{kg}\text{-min}$	6 hours	Heparin
Group B	40 $\mu\text{g}/\text{kg}$	1.0 $\mu\text{g}/\text{kg}\text{-min}$	6 hours	Heparin

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: Batch/Lot# A0004A
- Placebo, Batch/Lot# A0005A
- Heparin Sodium Injection, USP,
- LyphoMed® Heparin Sodium Injection, USP,

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 60 minutes pre-infusion; 30, 60, and 90 min and 2, 4, and 6 hours during infusion; 10, 30, and 60 minutes and 2, 4, and 6 hours post-infusion.

Pharmacodynamics: Platelet aggregation and Simplate bleeding time

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: eligibility violations - 2
heparin administration violations - 1

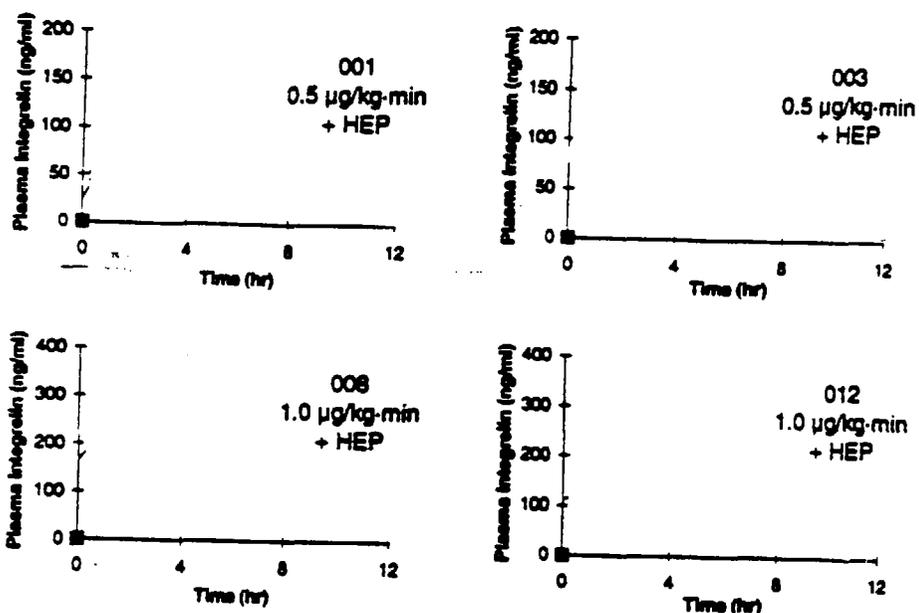
RESULTS

Pharmacokinetics:

Integrilin plasma concentration: The pharmacokinetic parameters for Integrilin are summarized in the table below.

Group	AUC (ng-hr/mL)	CL (mL/kg-hr)	Vss (mL/kg)	Css (ng/mL)	T1/2 (hr)
Integrilin 20 µg/kg + 0.5 µg/kg-min and heparin (Group A)					
Mean ± SD	992 ± 81.0	203 ± 16.7	438 ± 65.4	138 ± 13.7	1.53 ± 0.23
Range					
N	4	4	4	4	4
Integrilin 40 µg/kg + 1.0 µg/kg-min and heparin (Group B)					
Mean ± SD	2050 ± 476	204 ± 43.7	512 ± 154	275 ± 65.1	1.72 ± 0.32
Range					
N	4	4	4	4	4

Typical plasma concentration vs. time curves are presented below.



Legend: The experimental plasma concentration of Integrin over time is shown as the symbols and solid curve is estimated from the best fit result of the sum of a complementary exponential and the exponential. Note the different scales on the two treatment groups.

The rising concentration during the infusion indicates that the bolus doses were not sufficient to establish steady state levels.

The overall mean (\pm SD) plasma half-life was 1.63 hours (\pm 0.27). The overall mean volume of distribution and plasma clearance were 475 mL/kg (\pm 116) and 204 mL/kg-hr (\pm 306), respectively. The mean C_{ss} and AUC values were 138 ng/mL and 992 ng-hr/mL for Group A, and 274 ng/mL and 2050 ng-hr/mL for Group B, respectively, suggesting that the pharmacokinetics of Integrilin are proportional in the range of doses used in this study.

Pharmacodynamics:

a. Simplatle Bleeding Time: The following is a summary of the mean effect on bleeding time expressed as maximum change from baseline (as a ratio of the baseline value).

	Placebo + Heparin	20 $\mu\text{g}/\text{kg}$ + 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ + Heparin (Group A)	40 $\mu\text{g}/\text{kg}$ + 1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$ + Heparin (Group B)
N	4	4	4
Mean	1.05	2.60	2.53
S.D.	0.21	0.68	0.97
Range			

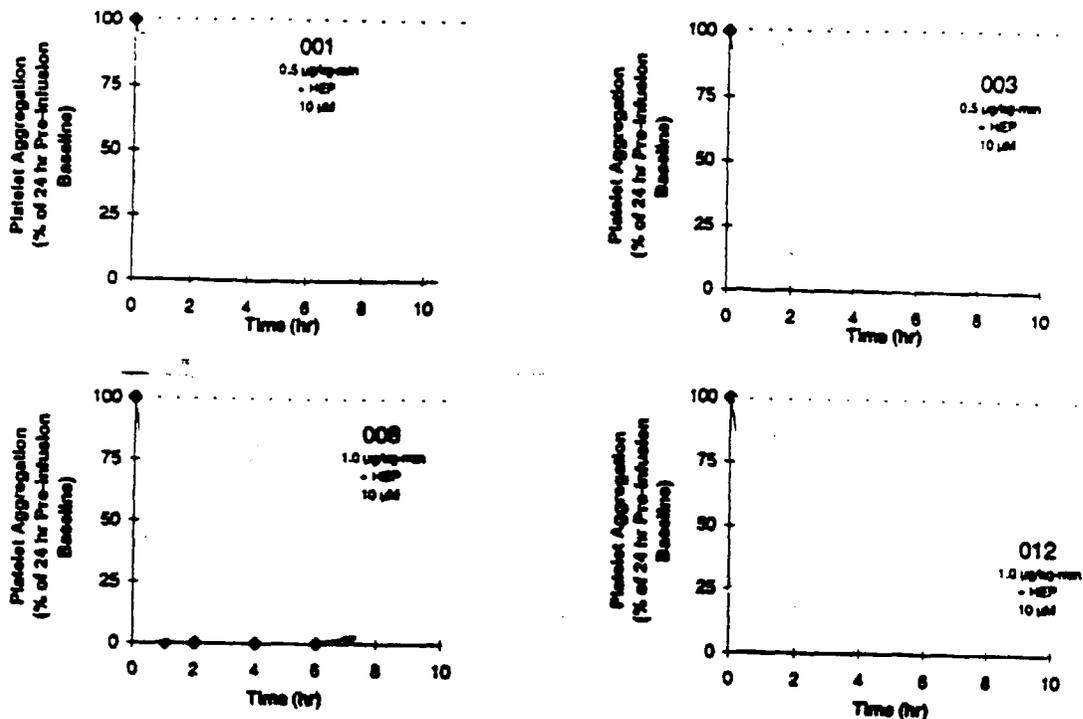
The subjects who received placebo plus heparin in this study showed no effect on bleeding time with a mean of 1.05. The maximum effect during Integrilin infusion was similar at the two dose levels of Integrilin. Integrilin at both doses produced a moderate increase in bleeding time to approximately 2.5 times the baseline values.

b. Platelet Aggregation: The following is the mean effect on platelet aggregation expressed as maximum change from baseline for the 10 μM ADP results.

	Placebo + Heparin	20 $\mu\text{g}/\text{kg}$ + 0.5 $\mu\text{g}/\text{kg}\cdot\text{min}$ + Heparin (Group A)	40 $\mu\text{g}/\text{kg}$ + 1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$ + Heparin (Group B)
N	4	4	4
Mean	92	7.8	4.3
S.D.	49	8.7	7.2
Range			

**APPEARS THIS WAY
ON ORIGINAL**

Selected results for platelet aggregation over time are presented below:



Legend: Platelet aggregation (ADP 10 µM) as a percent of 24 hr pre-infusion baseline. Symbols are experimental values and lines connect the data points. The dotted line indicates 100% (baseline value).

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

Pharmacokinetics: The overall mean (\pm SD) plasma half-life was 1.63 hours (0.27). The overall mean volume of distribution and plasma clearance were 475 mL/kg (\pm 116) and 204 mL/kg-hr (\pm 306), respectively. The mean C_{ss} and AUC values were 138 ng/mL and 992 ng-hr/mL for Group A, and 274 ng/mL and 2050 ng-hr/mL for Group B, respectively. However, this can only be a hypothesis in view of the inadequate assay.

The mean C_{ss} and AUC for Group A were almost one-half those for Group B, suggesting that the pharmacokinetics of Integrilin are proportional in the range of doses used in this study. Although the assay was inadequate, reasonable judgement of dose proportionality can be made with this study.

Pharmacodynamics: Integrilin at both doses, $20 \mu\text{g}/\text{kg} + 0.5 \mu\text{g}/\text{kg}\cdot\text{min}$ and $40 \mu\text{g}/\text{kg} + 1.0 \mu\text{g}/\text{kg}\cdot\text{min}$, produced a moderate but consistent increase in Simplate bleeding time to approximately 2.5 times the baseline values and a profound effect on ex vivo platelet aggregation with nearly complete inhibition during the infusion. Both effects returned toward baseline rapidly when the infusion was terminated. In the four volunteers administered the placebo plus heparin infusion there was no effect on either bleeding time or ex vivo platelet aggregation.

**APPEARS THIS WAY
ON ORIGINAL**

Study 92-008

Title: An open-label pharmacokinetic evaluation in post-menopausal female volunteers of Integrilin administered for ninety minutes by continuous IV infusion.

Study Dates: 6/4/92 - 6/24/92

Objectives:

- To assess the safety of Integrilin administered by a bolus dose of 90 $\mu\text{g}/\text{kg}$ followed by a continuous IV infusion at an infusion rate of 1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$ over 90 minutes in post-menopausal females.
- To evaluate the PK of Integrilin and the relationship between plasma concentrations and inhibition of platelet function as measured by platelet aggregometry and Simplate bleeding time in post-menopausal females.

Study Design: This was a single-center, open-label study in healthy post-menopausal women. Four healthy post-menopausal women with a mean age of 52 years (range 45-60) were enrolled and completed the study. All women were white. They received a 90 $\mu\text{g}/\text{kg}$ Integrilin bolus followed by a continuous IV infusion at a rate of 1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$ for ninety minutes.

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: , Batch/Lot# A0004A

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 60 min pre-infusion; 30, 60, and 90 min during infusion; 30 and 60 min and 2, 4, 6 and 24 hours post-infusion.

Pharmacodynamics: Platelet aggregation and Simplate bleeding time

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: ocular funduscopy not performed - 4
post-infusion physical exam not performed - 4

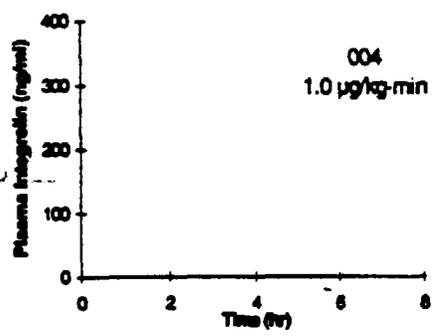
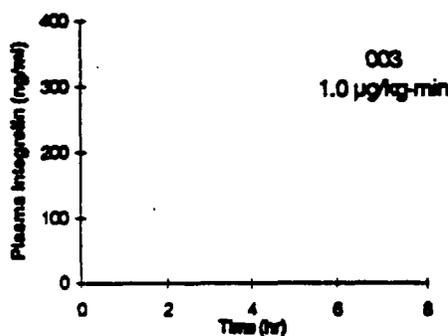
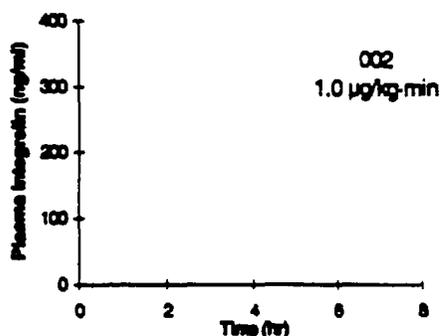
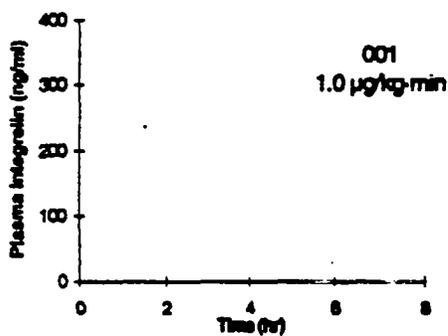
RESULTS

Pharmacokinetics:

Integrilin plasma concentration: The pharmacokinetic parameters for Integrilin are summarized below.

	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	C _{ss} (ng/mL)	T _{1/2} (hr)
Mean ± SD	1178 ± 136	157 ± 17.9	412 ± 73	213 ± 5.36	1.81 ± 0.20
Range					
N	4	4	4	4	4

The reliability of the C_{ss} estimates in this study is limited by the small number of subjects and the short infusion duration relative to the estimated half-life.



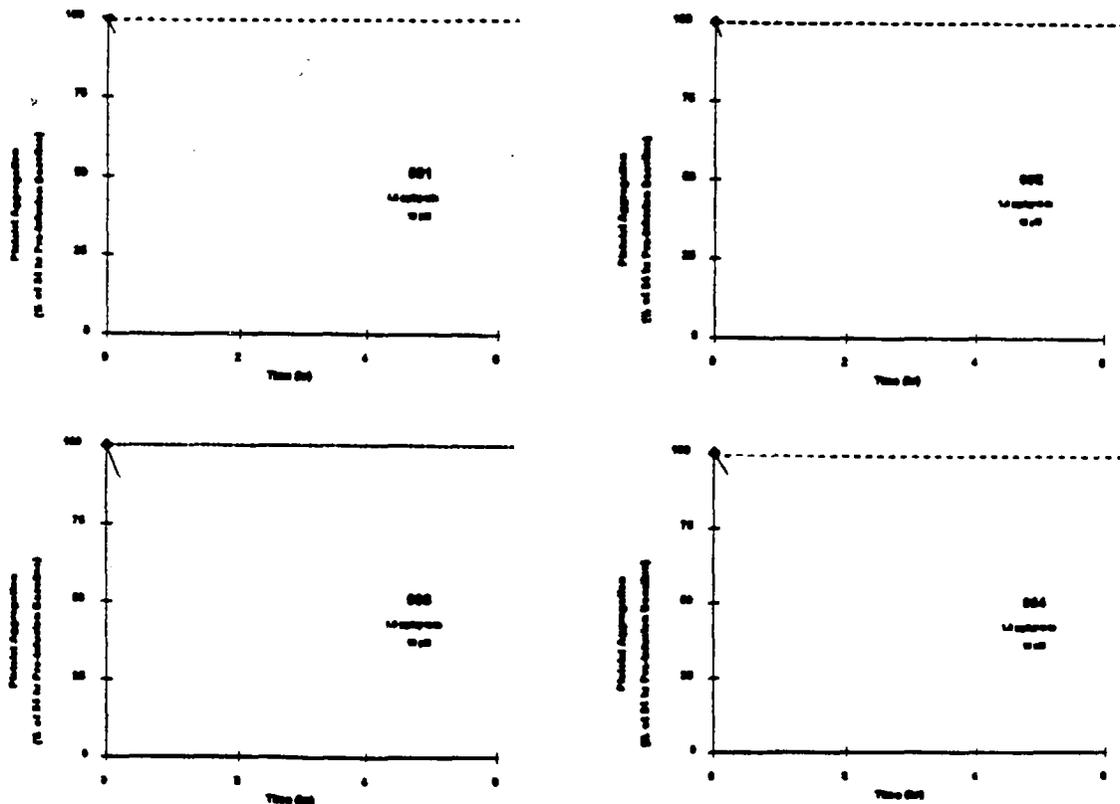
Legend: The experimental plasma concentration of Integrilin over time is shown as the symbols and solid curve is estimated from the best fit function.

The maximum plasma Integrilin concentrations observed near the end of infusion were 378 ng/mL, 337 ng/mL, 388 ng/mL and 268 ng/mL. It appears that the bolus dose of 90 $\mu\text{g}/\text{kg}$ was nearly sufficient in all four cases to achieve the steady state concentration associated with the infusion of 1.0 $\mu\text{g}/\text{kg}\text{-min}$ since there was only a small additional increase in plasma concentration during the infusion.

Pharmacodynamics:

a. Simplate Bleeding Time: The bleeding times were increased moderately in all four subjects when assessed at one hour into the infusion. The increase was less than twofold in all cases.

b. Platelet Aggregation: The following is the percent platelet aggregation relative to baseline over time for individual subjects.



Legend: Platelet aggregation (ADP 10 μM) as a percent of 24 hr pre-infusion baseline. Symbols are experimental values and lines connect the data points. The dotted line indicates 100% (baseline value).

Profound inhibition of platelet aggregation during the infusion was observed in all but one subject (004). This subject had a peak concentration of Integrilin lower than the other three. Platelet aggregation returned rapidly toward baseline when the infusion was terminated.

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions: In four post-menopausal female volunteers, the mean plasma half-life was 1.81 hours and ranged . The mean plasma clearance was 157 mL/kg-hr and values ranged The mean calculated value of C_{ss} was 213 ng/mL with a range . However, this can only be a hypothesis in view of the inadequate assay.

**APPEARS THIS WAY
ON ORIGINAL**

Study 94-020

Title: Pharmacokinetics, pharmacodynamics and safety of Integrilin in subjects with moderate renal failure.

Study Dates: 8/5/94 - 2/6/95

Objective: To evaluate the pharmacokinetics, pharmacodynamics and safety of Integrilin administered by simultaneous bolus and continuous infusion to subjects with moderate renal failure compared to age-matched controls.

Study Design: The study was conducted in two parts. A total of 16 subjects were involved in the study.

Part I was an open-label, single-dose study, to determine the plasma clearance of Integrilin in three subjects with moderate renal insufficiency, defined as creatinine clearance of 30-60 mL/min. Three women with a mean age of 63.7 years (range 62-65) were enrolled. A single 70 $\mu\text{g}/\text{kg}$ bolus of Integrilin was administered. This dose was based on a target plasma concentration of Integrilin of 550 ng/mL. Data from Part I was used to calculate the bolus and continuous infusion rate for Part II.

Part II was an open-label study of a single IV bolus followed by a continuous IV infusion of Integrilin. The bolus dose, infusion rate and duration were determined from Part I of the study and was a 50 $\mu\text{g}/\text{kg}$ IV bolus followed by 0.35 $\mu\text{g}/\text{kg}\cdot\text{min}$. This stage involved six subjects with moderate renal insufficiency (creatinine clearance of 30-60 mL/min) and an additional seven age-matched healthy subjects (creatinine clearance > 70 mL/min).

In Part II the 6 renally impaired subjects were 5 women and 1 man with a mean age of 62.8 years (range 59-65). All subjects had a creatinine clearance within the required rate of 30-60 mL/min with a mean of 52.7 mL/min. The age-matched healthy subjects in Part II were 1 woman and 6 men with a mean age of 56.7 years (range 44-64). All subjects had creatinine clearance values above 70 mL/min with a mean of 81.5 mL/min.

Treatment/Group	Dose	Dosage Form	Strength	Batch/Lot Size	Batch/Lot#
Part One-Renal	70 µg/kg	bolus	2 mg/mL	110 L	E0019A
Part Two-Renal	50 µg/kg 0.35 µg/kg-min	bolus infusion	2 mg/mL 0.5 mg/mL	110 L 350 L	E0019A D0016A
Part Two-Normal	50 µg/kg 0.35 µg/kg-min	bolus infusion	2 mg/mL 0.5 mg/mL	110 L 350 L	E0019A D0016A

** Represents To-Be-Marketed dosage form.

PK/PD Sampling Times:

Plasma samples for Integrilin assay:

Part I: Pre-infusion; 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-infusion

Part II: Pre-infusion, 6, 12, 18, 21, and 24 hours post-bolus administration

Urine:

Part II: Pre-infusion, 0-6, 6-12, 12-18, 18-21, and 21-24 hours post-bolus administration

Pharmacodynamics: Platelet aggregation

Analytical Methodology: Please refer to page 7 of this review.

Data Analyses: Please refer to pages 7-18 of this review.

Protocol Deviations:

Part I: protocol-specified menu not used - All
 Blood storage violations - All
 Exercise prohibition violation - 1
 Caffeine consumption violation - 1
 Vital signs not checked as required - 2
 Under dosage for weight - 1

Part II: Lab sample violations - All
 Pump setting errors - 3
 Infusion stopped early - 1

**APPEARS THIS WAY
ON ORIGINAL**

RESULTS:

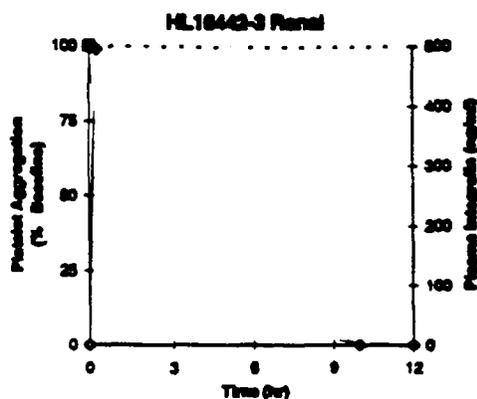
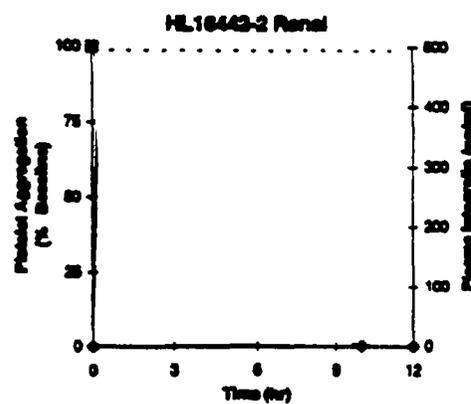
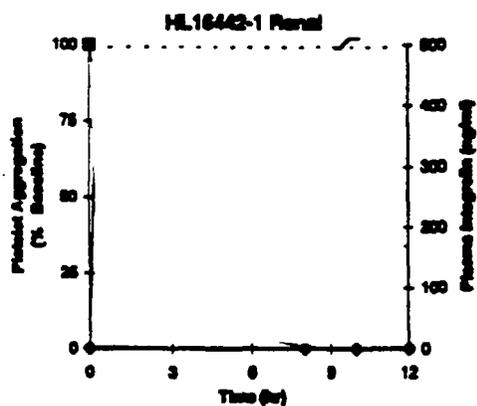
Part I: The pharmacokinetic parameters for Integrilin are summarized below.

Integrilin 70 $\mu\text{g}/\text{kg}$ - Renal

Parameters	AUC (ng-hr/mL)	CL (mL/kg-hr)	Vss (mL/kg)	T1/2 α (hr)	T1/2 β (hr)
Mean	1019	70.1	210	0.31	2.40
S.D.	166	12.6	15.8	0.29	0.56
Range					
N	3	3	3	3	3

From the single bolus, the best fit to the experimental data was a bi-exponential function.

The mean plasma half-lives were 19 min and 2.40 hrs for T1/2 α and T1/2 β , respectively. The plasma clearance had a mean value of 70.1 mL/kg-hr. The mean steady-state volume of distribution Vss was 210 mL/kg.



The Integrilin plasma concentration had a mean value of 443 ng/mL at the first measurement at 15 min post-injection. Levels decreased rapidly to a mean of 248 ng/mL at 1 hr and 50 ng/mL at 6 hrs.

Platelet aggregation decreased to a minimum to 20%-28% of baseline at 1 hr after bolus administration and then returned rapidly toward pre-dose baseline levels.

Part II: The pharmacokinetic parameters for Integrilin are summarized below.

Integrilin 50 μ g/kg + 0.35 μ g/kg-min - Renal

Parameters	Css (ng/mL)	AUCt (ng-hr/mL)	CLp (mL/kg-hr)	CLr (mL/kg-hr)	CLr/CLp (%)
Mean	223	4505	80.9	42.0	40.6
S.D.	44	911	36.7	12.7	4.5
Range					
N	6	6	6	6	6

* Not included in mean value

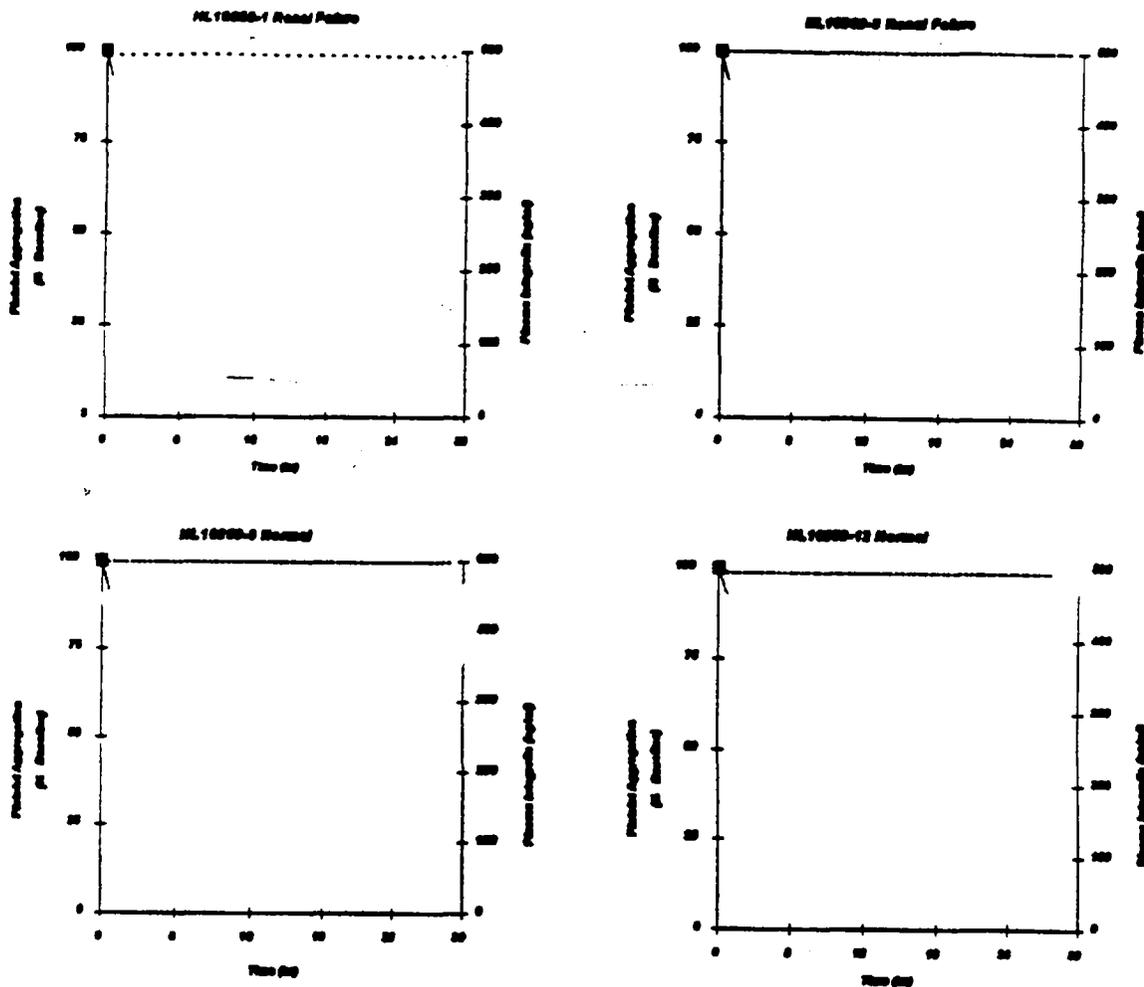
Integrilin 50 μ g/kg + 0.35 μ g/kg-min - Normal

Parameters	Css (ng/mL)	AUCt (ng-hr/mL)	CLp (mL/kg-hr)	CLr (mL/kg-hr)	CLr/CLp (%)
Mean	272	5624	85.1	40.7	49.2
S.D.	93.6	1984	27.6	11.1	9.2
Range					
N	7	7	7	7	7

The C_{ss} values were calculated as the average of all plasma concentrations measured during the 24-hour infusion.

The mean C_{ss}, CL_p, CL_r and CL_r/CL_p values between renally impaired and age-matched healthy subjects were not significantly different.

The following figures show the selected curves for Part II for Integrilin plasma concentration over time and for platelet aggregation over time in parallel.



Legend: Platelet aggregation (ADP 20 μ M) as a percent of pre-infusion baseline (solid symbols, left axis) and Integrilin plasma concentration over time (open symbols, right axis). Symbols for platelet aggregation and plasma concentration represent experimental data. Lines connect data points. The dotted indicates 100% (baseline value) for platelet aggregation.

Platelet aggregation was reduced to a minimum value of 26% or less of baseline during the infusion. The values remained low throughout the infusion and increased rapidly toward baseline once the infusion was stopped.

The amount of Integrilin measured in urine is reported for the combined amount of Integrilin and its deamidated breakdown product for all subjects in Part II. For renal insufficiency subjects the mean total amount excreted during the 24-hr infusion was 15.5 mg. For healthy subjects the mean amount excreted was 19.5 mg. The mean values as a percent of the dose administered were 36% for renally impaired subjects and 43% for healthy subjects. These values underestimate the renal excretion of Integrilin as parent compound and its deamidated breakdown product since the period of urine collection did not extend beyond the end of the infusion.

PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

PK: There are no apparent differences in mean pharmacokinetic parameters between the really impaired and normal subjects, although the difference in estimated creatinine clearance was approximately 30 mL/min between the two groups. However, in view of the inadequate assay there is doubt cast on conclusions drawn from comparisons across populations.

The total amount of Integrilin and its deamidated product which was excreted in the urine during the 24-hour infusion was comparable between the two groups; it averaged 15.5 mg and 19.5 mg for the renally impaired and healthy subjects, respectively. The mean values as a percent of the dose administered were 36% for renally impaired subjects and 43% for healthy subjects.

PD: Ex vivo platelet aggregation was reduced to 26% or less from baseline during the infusion in both renally impaired and the healthy subjects. The values remained low during the infusion and increased rapidly toward baseline once the infusion was terminated.

**APPEARS THIS WAY
ON ORIGINAL**

Study 92-009

Title: A randomized, double-blind trial of Integrilin versus placebo in the setting of coronary angioplasty.

Investigator and Site: multiple

Study Dates: 12/17/92 - 4/4/93

Objectives:

- To investigate the efficacy of Integrilin as therapy for the reduction of the incidence of the composite endpoint of death, non-fatal myocardial infarction and urgent intervention during and following coronary angioplasty.
- To establish the safety profile of Integrilin in the setting of coronary angioplasty.
- To provide preliminary estimates of treatment effects to be used in the design of a subsequent phase III clinical study.
- To provide measures of pharmacokinetics, the effects on platelet aggregation and bleeding times, and the immunogenicity (by measurement of anti-Integrilin antibodies) of Integrilin in a subset of patients enrolled at two centers.

Study Population: A total of 150 patients scheduled for coronary angioplasty (PTCA) were recruited from 15 investigational sites. At 2 sites, Duke University and the Cleveland Clinic, 27 patients were included in a pharmacokinetic subgroup. Plasma samples for Integrilin assay were obtained from 24 patients. Demographics for these 24 patients are presented in Table 1. There were 21 males and 3 females with a mean age of 59.0 years (range 40-75) and a mean body weight of 84.4 kg. Patients 02-001, 02-002, and 02-020 were originally included in the pharmacokinetic study but no plasma samples were obtained.

Study Design: This was a Phase II randomized, double-blind, placebo-controlled, multi-center clinical study in patients undergoing coronary angioplasty. One hundred fifty patients were enrolled in two groups of 75 patients each, Groups A and B. Each group was randomly assigned in a 2:1 ratio to receive either Integrilin or matching placebo administered by intravenous bolus (90 $\mu\text{g}/\text{kg}$) followed by a continuous infusion (1.0 $\mu\text{g}/\text{kg}\cdot\text{min}$). Treatment in each group was initiated 30 minutes before the start of the angioplasty procedure and continued throughout the procedure. The duration of post-angioplasty infusion was either four hours (for Group A) or twelve hours (for Group B) starting from the completion of the coronary angioplasty procedure. All patients received aspirin (325 mg) prior to the procedure and on the day following the procedure. All patients also received a bolus of heparin to achieve and maintain an activating clotting time (ACT) of between 300 and 350 seconds during the procedure.

Test Products:

- Integrilin, 2 mg/mL, Batch/Lot Size: , Batch/Lot# C0006A
- Placebo, Batch/Lot# C0007A

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 1 hour during infusion and immediately before the end of infusion

Pharmacodynamics: Platelet aggregation and Simplate bleeding time and anti-Integrilin antibodies

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

Protocol Deviations: N/A

RESULTS

Pharmacokinetics:

Integrilin plasma concentration: Only two specimens were obtained from each of 22 patients for plasma Integrilin levels, precluding a formal pharmacokinetic analysis. However, from the average concentration at the fine time point in Group B, which would approximate the steady state concentration, the average plasma clearance in these 7 patients was 201 mL/kg-hr from the following relationship:

$$CL = \text{Infusion Rate} \div C_{ss}$$

Plasma samples were to have been obtained from each patient one hour into the infusion and at the end of the 4 hour (Group A) or 12 hour (Group B) infusion. The actual mean sampling times for Group A were 2.17 hours and 5.07 hours, and for Group B, those were 2.39 hours and 13.34 hours, respectively. The mean results and corresponding time points from the two Groups are presented in the following table.

	Group A		Group B	
N	13	12	9	7
Mean Time (hr)	2.17	5.07	2.39	13.34
Mean Conc. (ng/mL) (range)	278	206	192	299
S.D. (Conc.)	181	126	124	170

The plasma Integrilin concentrations in both groups at both time points were highly variable.

Pharmacodynamics:

a. Simplate Bleeding Time: The Simplate bleeding time was measured in a subset of 29 patients. The mean bleeding time was prolonged approximately a 2-4 fold during the Integrilin infusion in patients who received Integrilin. Mean bleeding times for placebo-treated patients did not change appreciably. The bleeding times had begun to return to baseline in the combined Integrilin group within 15 or 60 minutes of stopping study drug.

b. Platelet Aggregation: Platelet aggregation was measured using 20 μ M ADP as an aggregant in a subgroup of 28 patients, 20 Integrilin-treated and 8 placebo-treated. Platelet aggregation was lower than 20% of baseline in the combined Integrilin-treated group both at 1 hour into the infusion and at the end of the infusion (16.6% and 14.1%, respectively). Mean platelet aggregation in the combined placebo group remained slightly above baseline at both time points. Mean platelet aggregation had returned to 63% of baseline within 4 hours of discontinuing Integrilin.

PK/PD Relationship: The data in terms of the number of data points for Integrilin concentration and inhibition of ex vivo platelet aggregation were not sufficient for formal PK/PD analysis.

Conclusions: Only two specimens were obtained from each of 22 patients for plasma Integrilin levels, precluding a formal pharmacokinetic analysis. However, from the average concentration at the final time point in Group B, which would approximate the steady state concentration, the average plasma clearance in these 7 patients was 201 mL/kg-hr. However, this can only be a hypothesis in view of the inadequate assay.

**APPEARS THIS WAY
ON ORIGINAL**

Study 93-012

Title: A randomized, double-blind, placebo-controlled evaluation of the safety, pharmacodynamics and pharmacokinetics of different dosing regimens of Integrilin plus heparin in patients with coronary artery disease and scheduled to undergo coronary angioplasty.

Investigator and Site: Multiple

Study Dates: 7/16/93 - 11/6/93

Objectives:

- To evaluate the PK/PD of various dosing regimens of Integrilin in patients undergoing coronary angioplasty.
- To determine the acute hemostatic effects of various doses of Integrilin combined with heparin.
- To evaluate the safety of Integrilin in patients undergoing coronary angioplasty.

Study Population: To be considered for enrollment in this study, patients were required to have a diagnosis of coronary disease documented by cardiac catheterization, and were to be scheduled for coronary angioplasty. Fifty-two of the 73 patients randomized with a diagnosis of coronary artery disease and scheduled for PTCA participated in the pharmacokinetic study. One of the 52 patients (#1009) only received Integrilin for 2 hours; he was not included in the pharmacokinetic analyses presented below. Integrilin plasma levels were measured in patients assigned to 4 different dosing regimens described below in Study Design. Groups C and G consisted of 6 females and 10 males with an overall mean age of 57.6 years (range 39-76 years). Group D consisted of 3 males with mean age 59.0 years (range 46-65 years). Groups E and F consisted of 8 females and 19 males with an overall mean age of 58.6 years (range 36-72 years). Group A consisted of 4 males with mean age 51.3 yr (range 34-71 yr). The gender, age and weight are listed in Table 1 for each patient and summarized by each treatment group. Also, included in Table 1 is the dose administered to each patient: bolus and infusion rate, duration and total dose.

Study Design: This was a Phase II randomized, placebo-controlled, multi-center investigation in patients with coronary artery disease (CAD) undergoing percutaneous transluminal coronary angioplasty (PTCA) with a marketed device. Patients received aspirin (325 mg) prior to study drug administration and daily thereafter, as well as heparin. The investigation was conducted at four sites. Each patient received an intravenous bolus dose of Integrilin followed by a continuous infusion of Integrilin for 18-24 hours based on the assigned dosage group as follows:

Dose Groups*	Bolus Dose ($\mu\text{g}/\text{kg}$)	Infusion Rate ($\mu\text{g}/\text{kg}\cdot\text{min}$)
D	90	0.75
C, G	135	0.5
E, F	135	0.75
A	180	1.0

* Per Amendment 1, Dose Group B was deleted from the study protocol
Dose Groups A, C, D and E were double-blind, Groups F and G were open-label

Test Products:

- Integrilin, 2 mg/mL and 0.5 mg/mL, Batch/Lot Size: Batch/Lot# C0008A
and D0011A
- Placebo, Batch/Lot# C0007A
- Bayer® Children's Chewable Aspirin,

- Heparin Sodium Injection, USP,
- LyphoMed® Heparin Sodium Injection, USP,

PK/PD Sampling Times:

Plasma samples for Integrilin assay: 0.25, 0.5, 1, 2, 4 and 12 hours during infusion; infusion termination; 0.25, 0.5, 1, 2, 4, 8, and 12 hours post-infusion.

Pharmacodynamics: Platelet aggregation and Simplate bleeding time.

Analytical Methodology: Please refer to page 8 of this review.

Data Analyses: Please refer to pages 8-9 of this review.

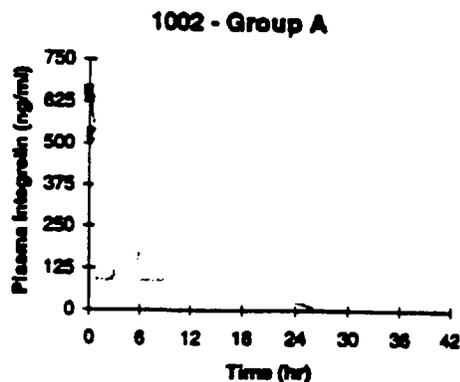
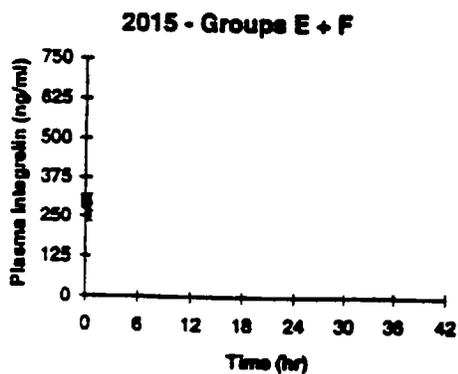
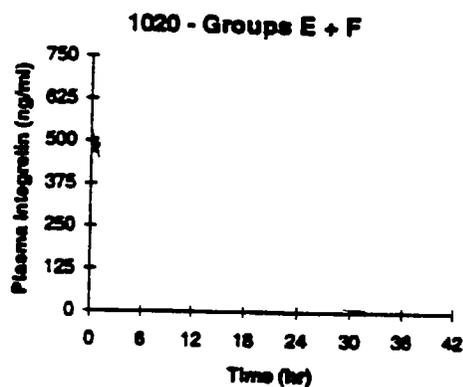
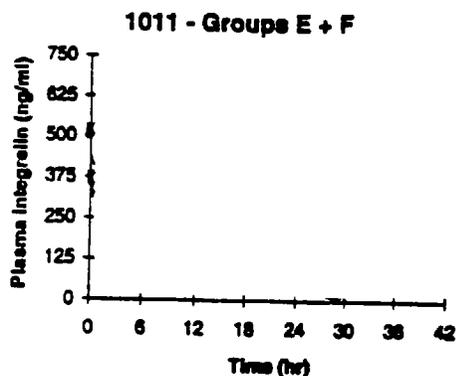
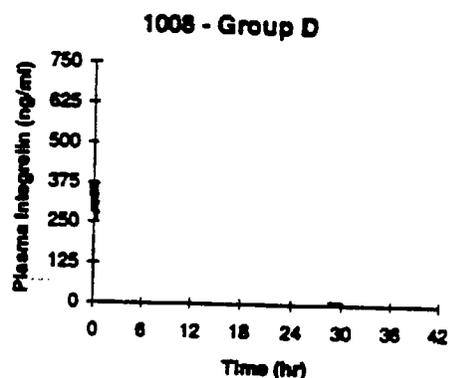
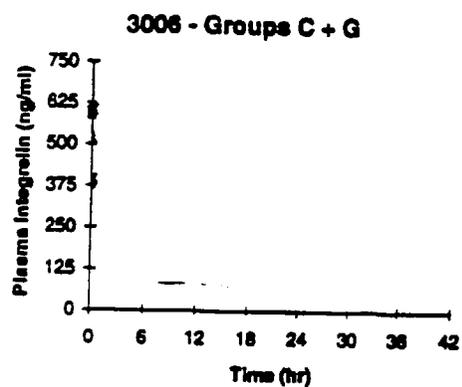
Protocol Deviations: 21 eligibility violations

**APPEARS THIS WAY
ON ORIGINAL**

RESULTS

Pharmacokinetics:

Integrilin plasma concentration: Selected plasma concentration versus time plots are presented below for six patients representing the four dose groups.



Legend: The experimental plasma concentration of Integrilin over time is shown as the symbols and the solid curve is from the best fit function.

The initial concentration of Integrilin at 15 minutes was higher than all later sample times, indicating that the bolus dose was more than sufficient to achieve the steady-state plasma concentrations associated with the subsequent infusion rate in all dose groups. Plasma levels then declined rapidly to steady state between the 4 hour and 12 hour samples.

The pharmacokinetic parameters for Integrilin are summarized below.

Regimens	C _{ss} (ng/mL)	AUC (ng-hr/mL)	CL (mL/kg-hr)	C ₀ * (ng/mL)	V _{ss} (mL/kg)	T _{1/2} (hr)
Group C & G: 135 µg/kg + 0.5 µg/kg-min						
Mean	254	6854	124	470	413	2.43
Range						
N	16	16	16	16	16	16
Group D: 90 µg/kg + 0.75 µg/kg-min						
Mean	174	4307	253	209	1046	3.34
Range						
N	4	4	4	4	4	4
Group E & F: 135 µg/kg + 0.75 µg/kg-min						
Mean	367	8173	134	454	385	1.95
Range						
N	26	27	27	26	27	27
Group A: 180 µg/kg + 1.0 µg/kg-min						
Mean	458	10583	150	471	517	1.96
Range						
N	4	4	4	4	4	4

* C₀: initial plasma drug concentration following bolus dose.

All Groups

	C _{ss} (ng/mL)	AUC (ng-hr/mL)	CL (mL/kg-hr)	V _{ss} (mL/kg)	T _{1/2} (hr)
Mean	323	*	142	456	2.21
S.D.	138	*	54.8	266	1.00
N	50	51	51	51	51

* The duration of infusion varied from patient to patient. Therefore, average AUCs are not meaningful.

The steady state plasma concentration associated with the range of doses used is a function of the infusion rate rather than the bolus dose. Though the infusion rate was the same in Group D and in Groups E & F, the dissimilar mean values are attributable to the small number of patients in Group D. The overall mean C_{ss} for all patients given an infusion rate of 0.75 µg/kg-min of Integrilin was 336 ng/mL.

The dose independent pharmacokinetic parameters, CL and V_{ss} and T_{1/2} were similar across the dose groups except for Group D into which only four patients were enrolled. The overall estimates of CL, V_{ss} and T_{1/2} were 142 mL/kg-hr, 456 mL/kg and 2.21 hours, respectively in this population of patients with ischemic heart disease.

Pharmacodynamics:

a. Simplate Bleeding Time: The following is a summary of the mean effect on bleeding time for each of the Integrilin infusion groups and placebo expressed as maximum change from baseline (as a ratio of the baseline).

	Placebo	Integrilin 90 & 0.75	Integrilin 135 & 0.50	Integrilin 135 & 0.75	Integrilin 180 & 1.0
N	8	4	15	24	3
Mean	1.58	1.66	2.36	2.59	3.68
SD	0.78	0.53	1.05	1.08	0.28

A dose-related effect was observed on Simplate bleeding time during the infusion with a 2.5 fold mean increase at a dose of 135 µg/kg as a bolus followed by an infusion of either 0.5 µg/kg-min or 0.75 µg/kg-min. The effect was more profound with a 3.68-fold increase at the 180 µg/kg bolus followed by an infusion of 1.0 µg/kg-min. At all dose levels, the bleeding time had returned toward baseline values when assessed one hour after terminating the infusion.

b. Platelet Aggregation: A profound effect on ADP-induced platelet aggregation during the infusion was observed at all dose levels. The effect was rapid with inhibition to less than 20% of the baseline values at the first sampling time of 15 minutes into the infusion and sustained throughout the infusion. Platelet aggregation returned toward baseline values after the infusion was terminated.

c. PK/PD Relationship: An analysis of the observed plasma concentration of Integrilin and simultaneously measured inhibition of platelet aggregation, combining data from this and other Phase I normal volunteer studies, is presented in pages 17-19 of this review.

Conclusions:

Pharmacokinetics: The estimates of steady state plasma concentrations of Integrilin associated with the infusion rates of 0.5 $\mu\text{g}/\text{kg}\text{-min}$, 0.75 $\mu\text{g}/\text{kg}\text{-min}$ and 1.0 $\mu\text{g}/\text{kg}\text{-min}$ were 254 ng/mL, 336 ng/mL and 458 ng/mL, respectively. The overall estimates of CL, Vss and T1/2 were 142 mL/kg-hr, 456 mL/kg and 2.21 hours, respectively in this population of patients with ischemic heart disease. However, this can only be a hypothesis in view of the inadequate assay.

Labeling Claims: The firm proposed the following labeling from this study:

PK: "For a 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion, steady-state plasma Integrilin concentrations are about 250 mg/mL and range from about 100 to 500 ng/mL. These plasma levels are achieved rapidly when the infusion is preceded by a 135 $\mu\text{g}/\text{kg}$ bolus."

PD: "The effect of an administered dose of Integrilin is observed within 15 minutes of the administration of a 135 $\mu\text{g}/\text{kg}$ intravenous bolus and is readily reversed 2-4 hours after stopping a continuous infusion of 0.5 $\mu\text{g}/\text{kg}\text{-min}$. Inhibition of ADP-induced ex vivo platelet aggregation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) showed a concentration-dependent effect with an IC50 (50% inhibitory concentration) of 93 ng/mL and IC80 (80% inhibitory concentration) of 292 ng/mL in citrated plasma."

"Administration of Integrilin by intravenous bolus and infusion caused a slight (1.5 to 2-fold) increase in bleeding time which is rapidly reversible upon discontinuation of the infusion."

Labeling Comments:

- The following statement, "For a 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion, steady-state plasma Integrilin concentrations are about 250 mg/mL and range from about 100 to 500 ng/mL. These plasma levels are achieved rapidly when the infusion is preceded by a 135 $\mu\text{g}/\text{kg}$ bolus." should be replaced by:

"For a 0.5 $\mu\text{g}/\text{kg}\text{-min}$ infusion, steady-state Integrilin plasma levels are achieved rapidly when the infusion is preceded by a 135 $\mu\text{g}/\text{kg}$ bolus."

- The following statement, "Inhibition of ADP-induced ex vivo platelet aggregation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) showed a concentration-dependent effect with an IC50 (50% inhibitory concentration) of 93 ng/mL and IC80 (80% inhibitory concentration) of 292 ng/mL in citrated plasma." should be replaced by:

"Inhibition of ADP-induced ex vivo platelet aggregation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) showed a dose-dependent effect."

Study 93-014

A. Population PK:

Title: Randomized, double-blind efficacy and safety evaluation of two dosing regimens of Integrilin versus placebo for reducing the complications of coronary angioplasty.

Investigator and Site: multiple

Study Dates: 11/30/93 - 1/8/96

Objective: The objective of a population pharmacokinetic substudy was to estimate the influence of patient and treatment variables, such as age, gender, race, renal function, hepatic function, alcohol abuse, smoking status and concomitant medications, on the plasma clearance of Integrilin.

Study Design: Patients who were scheduled to undergo urgent or elective coronary angioplasty with a marketed percutaneous coronary intervention device were eligible for enrollment. Patients were excluded if they were increased risk bleeding, had severe hypertension, had a history of stroke or CNS damage, might be pregnant, had participated recently in another trial or could not give written informed consent.

Eligible patients were randomly allocated to one of three treatments: 1) a bolus of Integrilin (135 $\mu\text{g}/\text{kg}$) followed by a continuous infusion of Integrilin at a dose of 0.5 $\mu\text{g}/\text{kg}\text{-min}$ (low dose group) for 20-24 hours; 2) an identical bolus of Integrilin (135 $\mu\text{g}/\text{kg}$) followed by a continuous infusion of Integrilin at a dose of 0.75 $\mu\text{g}/\text{kg}\text{-min}$ (high dose group) for 20-24 hours; or 3) a matching placebo bolus followed by a continuous infusion of placebo for 20-24 hours. The study drug was administered as a bolus followed by a continuous infusion initiated immediately prior to angioplasty. All patients initially received an intravenous heparin bolus of 100 units/kg followed by up to 2000 additional units every 15 minutes to maintain an elevation of the activated partial thromboplastin time (aPTT) of 2-3 times control. Unless contraindicated, aspirin (325 mg) was administered orally within 24 hours prior to the planned procedure and then once daily. Patients were followed until hospital discharge and were re-evaluated at 30 days and 6 months following enrollment.

Subjects: A total of 4010 patients were enrolled in this IMPACT II Trial, a Phase III clinical trial to determine the safety and effectiveness of Integrilin in patients undergoing percutaneous coronary angiography. Patients were randomized to treatment with an intravenous bolus of 135 $\mu\text{g}/\text{kg}$ of Integrilin followed by an infusion of either 0.50 $\mu\text{g}/\text{kg}\text{-min}$ or 0.75 $\mu\text{g}/\text{kg}\text{-min}$ for 24 hours, or a similar placebo regimen. Integrilin was administered to 2586 patients and a total of 1725 patients (1301 M, 424 F, mean age of 59.3 years, mean weight of 85.4 kg), 888 at the high dose and 837 at the low dose, had an evaluable plasma sample and were evaluated in a population pharmacokinetic analysis.

Plasma Samples: One plasma sample for Integrilin concentration was obtained from each patient immediately prior to terminating the infusion whenever possible.

Because only one plasma concentration was obtained from each patient, it was not possible to distinguish between intra-individual variability and inter-individual variability in the model. For this reason, the intra-individual variability was assumed to be represented by a CV of 25% and the value of the inter-individual variability was estimated subject to this constraint. Certain covariables, i.e. those close to being accepted with this assumption, were also tested using a CV of 35% to determine whether or not this assumption influenced the conclusions.

The covariables tested for their effect on the resulting estimates of Integrilin clearance included the patient's age, weight, gender, race, renal function, liver function (SGPT), alcohol abuse, smoking status and concomitant use of a variety of drugs. The renal function for each patient was determined by estimating the creatinine clearance based on age, ideal body weight and serum creatinine level using the method of Cockcroft-Gault.

A general description of the models used to estimate the population value of Integrilin clearance is as follows:

$$CL_i = f(\theta, X_i)$$

where:

θ is the vector of parameters,

X_i represents all concomitant data covariates of the i^{th} individual (e.g., age _{i} , weight _{i} , etc.), and

$f(\cdot)$ is a function of known form.

Evaluation of each covariable's contribution to the population estimate of Integrilin clearance was a stepwise procedure. Each covariable was tested initially by its separate inclusion in the model. The criterion of significance for inclusion in the model at this point was $p < 0.05$. The second step involved the stepwise addition into the model of those found initially to be significant by their separate inclusion. The criterion for significance at this step was $p < 0.01$. A "tentative model" was then constructed consisting of all covariates found significant at the second step. Finally, those found to be significant by stepwise addition were tested by their stepwise deletion from the "tentative model." At this final stage, those with a p value of < 0.001 were retained as significant in the "final model."

A description of UCSF pharmacokinetic data sets and NONMEM control file and output for final pharmacokinetic model are attached.

Formulations:

Treatment/Group	Dose	Dosage Form	Strength	Batch/Lot Size	Batch/Lot#
Integrilin Low Dose	135 µg/kg 0.5 µg/kg-min	bolus infusion **	2 mg/mL	35 L	D0014A
			2 mg/mL	35 L	D0015A
Integrilin High Dose	135 µg/kg 0.75 µg/kg-min	bolus infusion	2 mg/mL	110 L	E0019A
			0.75 mg/mL	350 L	D0018A
			0.75 mg/mL	350 L	E0020A
			0.50 mg/mL	350 L	D0011A
			0.50 mg/mL	350 L	D0016A
			0.50 mg/mL	350 L	D0017A
Placebo	-	bolus infusion	-	-	D0013A
					D0012A

** Represents To-Be-Marketed dosage form.

PK/PD Sampling Times:

Plasma samples for Integrilin assay: Immediately prior to termination of infusion in a subset of patients

Analytical Methodology: Please refer to page 7 of this review.

Protocol Deviations:

Any Exclusion	302 (7.8%)
Severe Hypertension	108 (2.8%)
History of Stroke	22 (0.6%)
PT > 1.2 Times Control	150 (3.9%)
Hematocrit < 30%	21 (0.5%)
Thrombocytopenia	3 (0.1%)
Creatinine > 4.0 mg/dL	1 (0.0%)
Gastrointestinal Bleeding	1 (0.0%)
Participated in Other Study	9 (0.2%)

Results:

Of the 2586 patients entered 20% did not have levels measured and 13% had plausible reasons for exclusion. A total of 1725 patients, 888 at the high dose and 837 at the low dose, had an evaluable plasma sample and were evaluated in a population pharmacokinetic analysis. A summary of plasma concentrations obtained from this study is shown in the following table.

Value	Low Dose (ng/mL)	High Dose (ng/mL)
N	888	837
Mean \pm SD	291 \pm 136	405 \pm 197
Median	275	391
Range		

The sample at steady-state provides a good estimate of clearance, however, the single per sample per patient precludes the estimation of residual error. By fixing residual error to 25% an estimate could be made of intersubject variation. Variation of the residual error (to 50%) has little effect on the point estimates of the pharmacokinetic parameters.

Following the first step in the analysis described above, the following covariates were rejected as not significant ($p > 0.05$):

atenolol	atropine	lisinopril
metoprolol	diphenhydramine	lidocaine
amlodipine	morphine	digoxin
nifedipine	nitrates	warfarin
enalapril	cefazolin	heparin

In the second step described above the following additional covariates were rejected as not significant ($p > 0.01$):

SGPT	tobacco use	diazepam
gender	alcohol abuse	midazolam
race	diltiazem	captopril

In the final step of the analysis (stepwise deletion of covariates) the following covariates were rejected as not significant ($p > 0.001$):

furosemide	fentanyl
------------	----------

Final model includes only creatinine clearance, age, weight.

Integrilin plasma clearance was found to be proportional to the patient's weight, and estimated creatinine clearance, and inversely proportional to age. The average patient in this study had an estimated Integrilin plasma clearance of 158 mL/min (median age 60 years, weight 84 kg and creatinine clearance 71.6 mL/min). For every 10 mL/min that a patient's creatinine clearance differs from 71.6 mL/min,

the clearance of Integrilin is predicted to change by about 4.6%, for every decade that a patient's age differs from 60 years, the clearance of Integrilin is predicted to change by about -5.3%, for every 10 kg that a patient's weight differs from 84 kg, the clearance of Integrilin is predicted to change by about 5.9%.

Comments: This can at best be a hypothesis which needs further support from studies using a validated assay.

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Appendix 5

NONMEM Control File and Output for Final Pharmacokinetic Model

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B. Mass Balance:

Objective: The mass balance substudy was designed to evaluate the pk and excretion profile of Integrilin. A mass balance study was performed in 30 patients enrolled at Duke University Medical Center.

Study Design: A total of 30 patients (20 men and 10 women) enrolled at Duke University Medical Center were selected to participate in the mass balance substudy. Their age and weight distributions were similar to those of the 4010 patients enrolled in the main study. Thirteen patients were randomized to low dose Integrilin, then patients to high dose Integrilin and seven patients to the placebo.

For this substudy, plasma samples were to be taken at 8, 16, and 24 hours during infusion and at 4, 8, and 12 hours post-infusion. In most cases only two determinations are available, one at 16 hours after the start of the infusion and one at the end of the infusion. The plasma samples taken at the end of the infusion are assumed to be at steady state. Urine samples for mass balance analysis were collected at 8, 16 and 24 hours during the infusion and at 8 and 16 hours post-infusion.

Results: The following is a summary.

Parameter	Inf. Rate ($\mu\text{g}/\text{kg}\text{-hr}$)	Exc. Rate ($\mu\text{g}/\text{hr}$)	C _{ss} (ng/mL)	CL _p (mL/kg-hr)	CL _r (mL/kg-hr)	CL _r /CL _p (ratio)
Low Dose Group						
N	13	13	13	13	13	13
Mean	30	851	282	125	40	0.32
SD	0	383	78	82	27	0.13
High Dose Group						
N	10	10	10	10	10	10
Mean	45	999	426	131	35	0.30
SD	0	714	161	89	23	0.21

Two methods were utilized to estimate the proportion of the administered Integrilin dose excreted in urine. The first method compared the total quantity of Integrilin and its deamidated breakdown product contained in all collected urine specimens with the total dose of Integrilin administered to the patient as a bolus and subsequent infusion. While the urine specimens were to have been collected up to 16 hours after the end of the infusion, the final specimen in many cases was obtained 8 hours or less after the infusion was terminated. These values were expressed as a percent of the total. The mean percent of Integrilin recovered in urine was 56.3% for the low dose group of 13 patients and 54.6% for the high dose group of 10 patients.

The second method was based on the assumption that all patients were at steady state with respect to plasma level and urinary excretion of Integrilin during the 6-8 hours just prior to terminating the infusion. The overall estimates for CL_p (based on a single plasma level determination at or near the end of the infusion) and CL_r (based on the duration of collection and quantity of Integrilin in the urine specimen obtained at the end of the infusion) are shown in the above table. This method compares the quantity of Integrilin recovered with the dose administered by infusion during the interval of urine collection just prior to terminating the infusion. The ratios of CL_r to CL_p were 0.32 and 0.30 for the low and high group, respectively. These estimates imply that only about one-third of the administered dose of Integrilin was excreted in the urine as Integrilin or its deamidation breakdown product at steady-state.

Labeling Claims:

PK: “In a 1725 patient population pharmacokinetic substudy within a large efficacy trial (IMPACT II), plasma clearance was proportional to the patient’s weight and estimated creatinine clearance, and inversely proportional to age. The expected changes in steady-state plasma Integrilin concentrations are modest and correspond to an increase of about 20% from age 40 to 80, an increase of 4-5% for each 10 mL/min decrease in creatinine clearance, and a decrease of about 25% between 60 kg and 100 kg of body weight. Since these parameters have only modest effects on plasma Integrilin levels, no dose adjustment of the 135 µg/kg bolus or the 0.5 µg/kg-min infusion are required for age, weight or renal function (up to a serum creatinine of 4.0 ng/dL).”

Drug Interactions: “In a population pharmacokinetic study performed within IMPACT II in 1725 patients, there was no evidence of a pharmacokinetic interaction between INTEGRILIN™ and the following coadministered drugs:

amlodipine	diazepam	fentanyl	metoprolol
atenolol	digoxin	furosemide	midazolam
atropine	diltiazem	heparin	morphine
captopril	diphenhydramine	lidocaine	nifedipine
cefazolin	enalapril	lisinopril	nitrates”

Labeling Comments:

- The following statement, “In a In a 1725 patient population pharmacokinetic substudy within a large efficacy trial (IMPACT II),.....no dose adjustment of the 135 µg/kg bolus or the 0.5 µg/kg-min infusion are required for age, weight or renal function (up to a serum creatinine of 4.0 ng/dL).” should be replaced by:

“Inadequate assay validation precludes conclusions being made concerning special populations such as the elderly, females and those with renal failure.”

- The following statement, "In a population pharmacokinetic study performed within IMPACT II in 1725 patients, there was no evidence of a pharmacokinetic interaction between INTEGRILIN™ and the following coadministered drugs:

amlodipine	diazepam	fentanyl	metoprolol
atenolol	digoxin	furosemide	midazolam
atropine	diltiazem	heparin	morphine
captopril	diphenhydramine	lidocaine	nifedipine
cefazolin	enalapril	lisinopril	nitrates" should be replaced by:

"Inadequate assay validation precludes conclusions being made concerning the drug interaction between INTEGRILIN™ and the following coadministered drugs:

amlodipine	diazepam	fentanyl	metoprolol
atenolol	digoxin	furosemide	midazolam
atropine	diltiazem	heparin	morphine
captopril	diphenhydramine	lidocaine	nifedipine
cefazolin	enalapril	lisinopril	nitrates "

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Protein Binding Study

The in vitro protein binding of Integrilin in human plasma was determined using an ultrafiltration technique. Table 1 shows the mean and raw data for protein binding of Integrilin at the concentrations of 0.05, 0.2, 0.5, 2 and 15 $\mu\text{g/mL}$. At the concentrations tested, the average extent of Integrilin binding to human plasma protein was 24%.

Plasma Concentration: 0.05 $\mu\text{g/ml}$			
Counts (cpm)/100 μl		% Bound	% Free
Prefiltration	Ultrafiltrate		
747	555	25.70	74.30
747	582	24.77	75.23
747	581	22.22	77.78
Mean	566	24.23	75.77
%CV	2.38	7.44	2.38
Plasma Concentration: 0.2 $\mu\text{g/ml}$			
Counts (cpm)/100 μl		% Bound	% Free
Prefiltration	Ultrafiltrate		
2918	2191	24.91	75.09
2918	2215	24.09	75.91
2918	2249	22.83	77.07
Mean	2218	23.88	76.02
%CV	1.31	4.15	1.31
Plasma Concentration: 0.5 $\mu\text{g/ml}$			
Counts (cpm)/100 μl		% Bound	% Free
Prefiltration	Ultrafiltrate		
7170	5518	23.04	76.96
7170	5470	23.71	76.29
7170	5490	23.43	76.57
Mean	5493	23.39	76.61
%CV	0.44	1.44	0.44
Plasma Concentration: 2 $\mu\text{g/ml}$			
Counts (cpm)/100 μl		% Bound	% Free
Prefiltration	Ultrafiltrate		
27881	20835	25.22	74.78
27881	21323	23.47	76.53
27881	21851	22.65	77.35
Mean	21236	23.78	76.22
%CV	1.72	5.52	1.72
Plasma Concentration: 15 $\mu\text{g/ml}$			
Counts (cpm)/100 μl		% Bound	% Free
Prefiltration	Ultrafiltrate		
204888	154871	24.34	75.66
204888	155674	23.95	76.05
204888	152457	25.51	74.49
Mean	154344	24.60	75.40
%CV	1.07	3.30	1.08
Mean percent binding and CV across concentrations			
Mean		24.00	76.00
%CV		1.90	0.80

APPENDIX II

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Summary of All Integrilin Studies

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Investigational Formulations

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Proposed Labeling

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Pharmacology Team Leader's Addendum to
Dr. I. Antonipillai's Pharmacology Review
of February 25, 1997

1. Noted.
2. Adequate preclinical studies of integrilin were conducted to characterize its pharmacology, acute toxicity (rats, rabbits and monkeys) and subacute toxicity (2-week and 4-week i.v. continuous toxicity studies in rats and cynomolgus monkeys) for its recommended human use by continuous i.v. infusion for about 24 hours following a bolus dose.
3. It produced transient thrombocytopenia in rabbits and baboons at i.v. infusion doses of 10 $\mu\text{g}/\text{kg}/\text{minute}$ or higher.
4. Clinical signs of acute toxicity were loss of righting reflex, dyspnea, ptosis and decreased muscle tone in rabbits and petechial hemorrhages in the femoral and abdominal area in cynomolgus monkeys.
5. In subacute toxicity studies, continuous i.v. infusion treatment produced petechial hemorrhages and focal hemorrhages in different visceral organs and skeletal muscles in cynomolgus monkeys at 5 $\mu\text{g}/\text{kg}/\text{minute}$ or higher while no such effects were noted at 1 $\mu\text{g}/\text{kg}/\text{minute}$ in monkeys or at 50 $\mu\text{g}/\text{kg}/\text{minute}$ dose in rats.
6. RECOMMENDATIONS:
 - a. Pharmacology recommends approval of this application.
 - b. As indicated, the marked portions in the attached sponsor's version of labeling should be replaced and/or expanded by the following. The placement of subsections should be in the same order as follows

I. PRECAUTIONS

a. "Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the carcinogenic potential of integrilin. Integrilin was not genotoxic in the Ames test, the mouse lymphoma cell (L 5178Y, TK⁺/-) forward mutation test, the human lymphocyte chromosome aberration test or the mouse micronucleus test. Integrilin by continuous intravenous infusion at total daily doses up

to 72 mg/kg/day (432 mg/m²/day, 13 times the recommended maximum total human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats."

b. "Pregnancy. Teratogenic Effects. Pregnancy Category B:

Teratology studies have been performed in pregnant rats by continuous intravenous infusion at total daily doses up to 72 mg/kg/day (432 mg/m²/day, 13 times the recommended maximum total daily human dose based on body surface area) and in pregnant rabbits at total daily doses up to 36 mg/kg/day (432 mg/m²/day, 13 times the recommended maximum total human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to integrilin."

II. "OVERDOSAGE

Integrilin by continuous intravenous infusion for 90 minutes at a total dose of 45 mg/kg was not lethal to rats, rabbits and monkeys (270 to 540 mg/m², 8 to 16 times the recommended maximum total human dose based on body surface area). Symptoms of acute toxicity were loss of righting reflex, dyspnea, ptosis and decreased muscle tone in rabbits and petechial hemorrhages in the femoral and abdominal areas in monkeys."

3/3/97

Jasti B. Choudary, Ph.D., B.V.Sc.
Pharmacology Team Leader
February 28, 1997

Attachment: Marked copy of Sponsor's draft labeling.

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Antonipillai
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd
HFD-345/Dr. Viswanathan

JBC/hw/3/3/97
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