

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

NDA: 20-718

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

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

4.0 Background

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

5.0 Study Design

Methods

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

Study Design

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

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

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

Table 5.0.1 Treatment groups in the PRIDE study^a.

Dose Group	Patient Enrollment (Target)	Study Drug Bolus ($\mu\text{g}/\text{kg}$)	Study Drug Infusion ($\mu\text{g}/\text{kg}\cdot\text{min}$)	Infusion Duration (hours)
A	20	Placebo	Placebo	24-72
B	20	135	0.75	24-72
C	40	180	2.0	24-72
D	40	250	3.0	24-72

a. from NDA volume 2.33 page 16.

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

5.1 Number of subjects/ randomization

The study was conducted at 14 sites.

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

5.2 Inclusion/ Exclusion Criteria

Inclusion Criteria

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

5.2 Inclusion/ Exclusion Criteria (cont)

Exclusion Criteria

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

5.3 Dosage/ Administration

Table 5.3.1 Dosing regimens in the PRIDE study^a.

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

a. from NDA volume 2.33 page 21.

Other cardiac medications were used as clinically indicated.

5.4 Duration/ Adjustment of Therapy

The following conditions were grounds for discontinuation from study

1. Clinical deterioration requiring emergency or urgent cardiac surgery.
2. Unusual or excess bleeding (defined in Appendix A of the protocol).
3. Ischemic stroke or new significant neural deficit or change in mental status.
4. Development of a platelet count <50,000/mm³.
5. Patient requirement for or receipt of a prohibited medication.
6. Serious adverse event possibly related to drug administration.

7. Serious adverse event which, in the view of the investigator, made it not in the best interests of the subject to continue.

5.5 Safety and Efficacy Endpoint Measured

Efficacy Assessment

1) Primary study efficacy endpoint

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

2) Secondary study efficacy endpoints

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

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

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

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

5.5 Safety and Efficacy Endpoint Measured (cont)

Safety Assessment

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

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

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

a. Pre-registration occurs when subject is planned for PTCA.

b. ACT = activated clotting time.

c. Data from NDA volume 2.33, Appendix A.

5.6 Statistical Considerations

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

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

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

6.0 Study Results

6.1 Patient Demographics & Baseline Characteristics

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

Table 6.1 Patient demographics from the PRIDE study^b.

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

a. Height & weight expressed as mean of all values.

b. Data from NDA volume 2.33, table 4.4.

6.1 Patient Demographics & Baseline Characteristics (cont)

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

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

a. Data from NDA volume 2.33, table 4.4.

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

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

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

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

6.2 Disposition of Subjects

Table 6.2.1 Disposition of subjects in the PRIDE study^a.

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

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

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

6.2b Protocol Violations & Deviations

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

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

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

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

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

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

6.2c Concomitant Therapies used after Trial Initiation

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

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

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

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

6.3 Pharmacokinetics of Integrilin from the PRIDE Trial

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

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

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

a. Data from NDA volume 2.36, section 2.3.1.

6.3 Pharmacokinetics of Integrilin from the PRIDE Trial (cont)

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

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

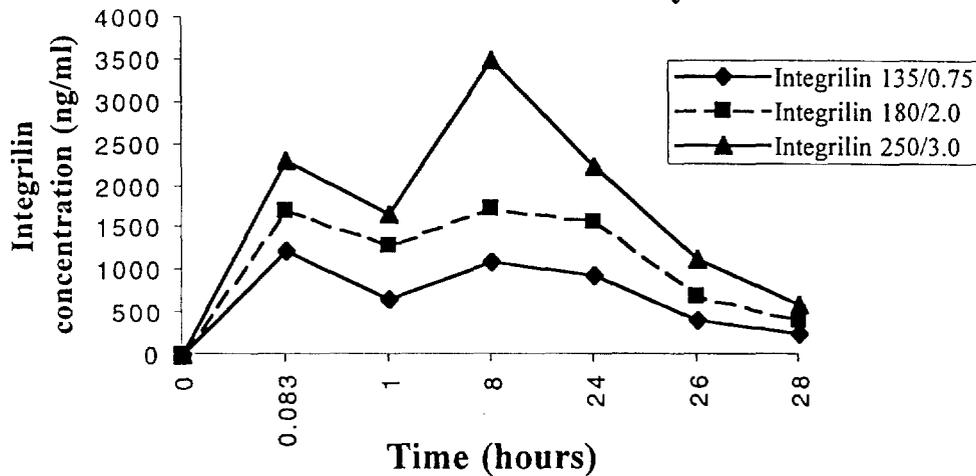
Parameter (mean \pm sem) ^b	Eptifibatide 135/0.75	Eptifibatide 180/2.0	Eptifibatide 250/3.0
c ₀ (ng/ml)	1267 \pm 273	1503 \pm 133	2513 \pm 241
C _{ss} (ng/ml)	724 \pm 34	1499 \pm 48	2351 \pm 82
t _{1/2} (hours)	2.48 \pm 0.51	2.81 \pm 0.52	2.58 \pm 0.44
AUC(l) (ng-hours/ml)	19546 \pm 932	38284 \pm 1210	59734 \pm 2063
CL (ml/min-kg)	1.04 \pm 0.049	1.33 \pm 0.042	1.27 \pm 0.044
V _d (l/kg)	0.201 \pm 0.025	0.259 \pm 0.027	0.238 \pm 0.025

a. Data from NDA volume 2.33, section 5.3.

b. C₀ = estimated initial plasma concentration; C_{ss} = plasma concentration at steady state; V_{dss} = steady-state volume of distribution; t_{1/2} = elimination half-life; CL = total body clearance; AUC(l) = area under plasma concentration-time curve extrapolated to infinity.

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

Figure 6.3.3 Dose-Time-Concentration Curve for PRIDE Study



6.4 Pharmacodynamics of Integrilin from the PRIDE Trial

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

6.4.1 Platelet aggregation

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

6.4.1 Platelet aggregation (cont)

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

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

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

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

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

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

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

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

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

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

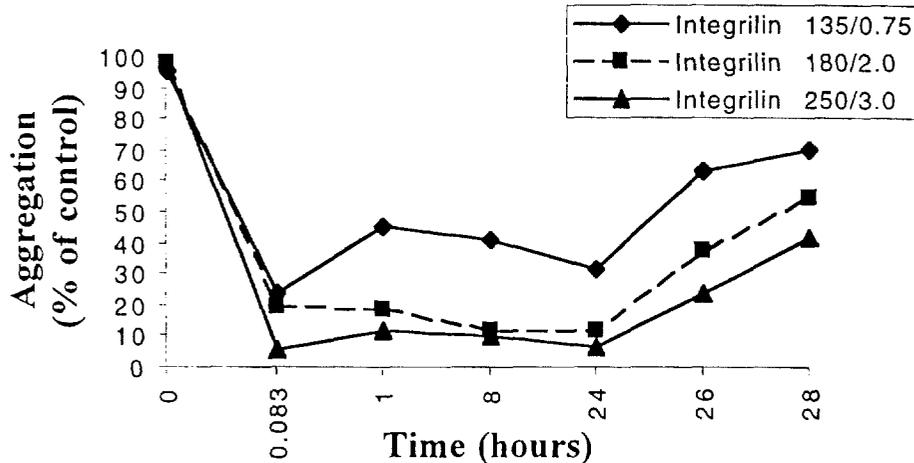
Time after start of infusion	Integrilin 135/7.0	Integrilin 180/2.0	Integrilin 250/3.0	Placebo
Baseline	100	100	100	100
5 minutes	26	24	20	108
1 hour	34	26	22	104
8 hours	27	25	22	101
24 hours	29	24	25	92
2 hours post-infusion	62	44	29	93
4 hours post-infusion	70	64	48	85

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

6.4.1 Platelet aggregation (cont)

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

Figure 6.4.4 ADP-induced Platelet Aggregation in PRIDE Study



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

Table 6.4.1.5 Fraction of subjects who achieved $\geq 80\%$ inhibition of platelet aggregation at the specified times from the PRIDE trial^a.

Conditions and Integrilin dose	1 hour	8 hours	24 hours
Integrilin 180/2.0 group			
ADP-induced in PPACK buffer	19/37 (51%)	30/36 (83%)	25/33 (76%)
ADP-induced in citrate buffer	35/36 (97%)	33/33 (100%)	31/31 (100%)
TRAP-induced in PPACK buffer	3/36 (8%)	5/34 (15%)	4/31 (13%)
TRAP-induced in citrate buffer	7/37 (19%)	9/34 (26%)	12/31 (39%)
Integrilin 250/3.0 group			
ADP-induced in PPACK buffer	31/35 (89%)	34/34 (100%)	33/34 (97%)
ADP-induced in citrate buffer	32/32 (100%)	28/29 (97%)	29/30 (97%)
TRAP-induced in PPACK buffer	8/33 (24%)	16/33 (48%)	13/32 (41%)
TRAP-induced in citrate buffer	13/31 (42%)	9/28 (32%)	11/29 (38%)

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

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

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

6.4.2 Platelet GP IIb/IIIa receptor occupancy

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

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

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

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

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

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

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

7.0 Safety Analyses of the PRIDE Trial Results

7.0.1 Clinical endpoints

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

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

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

7.0.2 Subject Deaths

There were no subject deaths during the trial.

7.0.3 Serious Adverse Events

Serious Bleeding Adverse Events

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

Table 7.0.3.1 Serious bleeding events in the PRIDE trial^a.

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

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

Serious Non-bleeding Adverse Events

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

Table 7.0.3.1 Serious bleeding events in the PRIDE trial^a.

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

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

7.0.4 Discontinuations Due to Adverse Events

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

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

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

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

Patient narratives for discontinued subjects

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

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

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

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

7.0.5 Adverse Events in the PRIDE study

7.0.5.1 Bleeding Adverse Events

TIMI Scale Bleeding

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

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

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

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

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

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

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

7.0.5.1 Bleeding Adverse Events (cont)

Bleeding Sites (per investigator)

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

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

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

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

Transfusions

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

7.0.5.2 Non-bleeding Adverse Events

Overall results for nonbleeding AEs are summarized below.

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

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

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

The most common AEs are shown in the table below.

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

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

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

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

7.0.5.3 Laboratory Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.0.5.3 Laboratory Adverse Events (cont)

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

Table 7.0.5.3.3 Abnormal CK levels in the PRIDE study^a.

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

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

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

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

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

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

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

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

8.0 PRIDE Trial Efficacy Summary

Pharmacokinetics

1. Integrilin plasma concentrations appear dose-proportional over the range of doses studied.
2. Integrilin elimination $t_{1/2}$ was approximately 2.6 hours, with a total body clearance of 1.2 ml/min-kg and a volume of distribution of 0.22 l/kg in the study population.

Pharmacodynamics

1. Integrilin binds reversibly to the GP IIb/IIIa receptor on human platelets in a dose- and concentration dependent fashion. The dose of Integrilin necessary to achieve 80% occupancy of the GP IIb/IIIa receptor on human platelets was 1723 ng/ml for PPACK-buffered, and 539 ng/ml for citrate-buffered platelets. These serum concentrations are achieved using the Integrilin doses studied in this trial.
2. Integrilin causes dose- and concentration-dependent inhibition of human platelet aggregation *ex vivo*. The dose of Integrilin necessary to cause an 80% reduction of platelet aggregation (IC_{80}) *ex vivo* is dependent on the agonist and buffer system used. For ADP-induced platelet aggregation, the IC_{80} is 811 ng/ml for PPACK-buffered and 504 ng/ml for citrate-buffered platelets. This was the primary analysis proposed by the sponsor. For TRAP-induced platelet aggregation, the IC_{80} values are approximately 3 time higher, and are not reproducibly achieved using the Integrilin doses studied in this trial.
3. The times of maximal Integrilin concentration correlates with the maximal inhibition of platelet aggregation, and are achieved immediately after the bolus and at steady state (8 hours after start of infusion). Inhibition of platelet aggregation at one time point intermediate between bolus and steady state (1 hour) demonstrated a lower degree of inhibition of platelet aggregation.
4. Rapid reversal of inhibition of platelet aggregation and receptor occupancy occur rapidly after discontinuation of Integrilin infusion, with values returning towards baseline by 4 hours. These findings are consistent with the pharmacokinetics of Integrilin.

9.0 PRIDE Trial Safety Summary

1. Few clinical events (MI, death, urgent revascularization, stroke, recurrent ischemia) occurred in the 30 day follow-up of the PRIDE trial, precluding any meaningful statistical analysis of the effect of Integrilin on these event rate. There was a lower incidence rate for definite/possible cardiac ischemia in the combined Integrilin group (6.4%) than in the placebo (18%) at 30 days (see table 7.0.1.1). No other differences in the incidence rates of the clinical events listed were noted.
2. No subjects died during the PRIDE trial or during the 30 day follow-up of the subjects with available data.
3. Subjects receiving Integrilin did not have a higher rate of serious adverse events, and no unusual or rare adverse events were associated with Integrilin use.
4. Subjects receiving Integrilin did have a higher incidence of minor bleeding and discontinuation due to bleeding, particularly in the 250/3.0 dose group.
5. No intracranial bleeding was reported in any subject in the PRIDE trial.
6. Subjects receiving Integrilin did not have a higher rate of non-bleeding adverse events relative to the placebo group. No rare or unusual adverse events associated with Integrilin administration were identified.
7. No hematological abnormalities were associated with Integrilin administration. No thrombocytopenia or neutropenia was reported.
8. The database is inadequate to assess the effect of Integrilin on the coagulation parameters due to the small number of subjects with data.
9. There was a higher incidence of the development of abnormally elevated SGOT/SGPT in the Integrilin group when compared with placebo. No chronic or severe liver damage was reported. No bilirubin values were submitted in the database.
10. There was a higher incidence of microscopic hematuria in the Integrilin group when compared with placebo.

10.0 PRIDE Trial Reviewer's Conclusions

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

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

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