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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-718/S-010

Medical Review(s)

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Memorandum

DATE: 4.24.01

FROM: Douglas C. Throckmorton, M.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Raymond Lipicky, M.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Integrilin (eptifibatide) financial disclosure information for ESPRIT trial.

PURPOSE OF MEMO

This memorandum reflects the findings of my review of the submitted financial disclosure information for the investigators of the ESPRIT trial. These materials, including FDA Form 3454, were submitted to the Agency on 6.29.00. Per these records, no investigator was the recipient of significant payments as defined in CFR 54.2(f). I find no evidence in the submitted information suggesting inappropriate or suspect financial arrangements between the sponsor (COR Therapeutics) and any of the investigators of the ESPRIT trial.

APPEARS THIS WAY
ON ORIGINAL

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Memorandum

DATE: 3.16.01

FROM: Douglas C. Throckmorton, M.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Raymond Lipicky, M.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Integrilin (eptifibatide) efficacy supplement for therapy after coronary stenting, NDA 20-718

PURPOSE OF MEMO

This memorandum reviews the materials submitted by COR Therapeutics in support of a proposed labeling change for Integrilin® (eptifibatide).

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0.0 Overall Summary

The ESPRIT trial was a randomized, placebo-controlled, double-blind trial comparing eptifibatide to placebo in patients hospitalized for percutaneous coronary intervention (PCI) with stent placement. Eptifibatide was given in a dosing regimen incorporating two boluses and an infusion for up to 48 hours after randomization. The primary endpoint in ESPRIT was the incidence of death, myocardial infarction, urgent target vessel revascularization (UTVR), and need for 'bail-out' therapy within 48 hours, as adjudicated by a Central Events Classification Committee (CEC) on the randomized population. Bail-out therapy refers to the use of open-label eptifibatide, which was available to the investigators when they felt that the clinical situation required the use of the product.

A total of 1024 patients were enrolled in the placebo group, and 1040 in the group receiving eptifibatide. In approximately 45% of these patients, PCI was performed for stable angina with or without abnormalities on functional testing, while around 50% of the patients had unstable angina. Of this latter group, 75% had not had symptoms within the previous 48 hours. A small fraction of the total entry population (5%) had an acute MI in the 7 days before enrolling. The two treatment groups were overall well-balanced with regard to critical demographics such as cardiac history and age, and with regard to the baseline characteristics including the extent of disease evident on angiogram.

At the end of 48 hours, the primary endpoint (death, MI, urgent target vessel revascularization, or use of 'bail-out' therapy) occurred in 10.5% of the placebo group (108 events), compared with 6.6% in the eptifibatide group (69 events). This difference corresponds a 37% reduction in the incidence of the primary endpoint with eptifibatide relative to placebo (p=0.0015). This difference extended to the individual parts of the endpoint with the exception of deaths, where too few occurred for meaningful comparison (3 total through 48 hours). For the endpoint of death or MI, eptifibatide reduced its incidence at 48 hours by 40%. Very few patients received bail-out therapy (1-2%), although more received it in the placebo group. Approximately 90% of the events at 48 hours were MIs, largely detected through the protocol-specified measurement of CPK levels through the first 24 hours after PCI. These samples were analyzed centrally, and not available to the investigators. As a result, the investigators identified fewer MIs than the CEC (88 fewer at 48 hours), and there was no significant difference between the two treatment groups for the primary endpoint or death/MI as identified by the investigators.

The reduction in the incidence of the primary endpoint in the eptifibatide group persisted through 30 days, where a 36% reduction in the incidence of the primary endpoint was seen in the eptifibatide group relative to placebo (120 events, 11.7% in placebo; 78 events, 7.5% in eptifibatide, p=0.0011). The effect of eptifibatide on the primary endpoint was consistent across a variety of sub-group analyses, including age, gender and medical history at entry. Relatively few non-white patients were enrolled, limiting the trial's power to assess the effect of eptifibatide in this population.

With regard to safety, increased bleeding was seen in the eptifibatide group. However, when compared with trials that utilized higher doses of heparin (especially the IMPACT-II trial), there was less bleeding overall in the ESPRIT trial in both treatment groups. This suggests that the lowered heparin dose used, in combination with other changes in clinical practice as regards to hemostasis, can decrease the overall rate of bleeding adverse events in this population. Too few life-threatening bleeding events were reported to compare the impact of the dosing changes on their incidence. The incidence of thrombocytopenia was increased slightly in the eptifibatide group.

In conclusion, ESPRIT provides robust support for the use of eptifibatide in patients undergoing PCI with stent placement using the revised dosing regimen, including the use of a lower dose of heparin. Proposed labeling changes are to be found in Appendix Five.

1.0 Materials Used in Review

1. NDA 20-718, SE8, ESPRIT clinical supplement (paper copy and electronic format).
2. My earlier review of the PRIDE trial, dated 1.9.98.
3. Statistical Review and Evaluation of ESPRIT by James Hung, Ph.D., dated 1.08.01.
4. Pharmacokinetics Review of ESPRIT by Gabriel Robbie, Ph.D., dated 2.01.01.
5. Data submissions by sponsor at request of reviewer dated 2.5.01, 2.27.01, 3.09.01 and 3.14.01.

2.0 Background

Two aspects of the ESPRIT trial planning require comment before reviewing the data: the rationale for the trial, and the discussions concerning the ethics of a placebo-controlled trial using intravenous IIb/IIIa inhibitor.

With regard to the rationale for the trial, the ESPRIT study (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) had as its primary objective to investigate the clinical efficacy of a change in eptifibatide dosing consisting of two boluses and a constant infusion, in patients undergoing percutaneous coronary intervention (PCI) with cardiac stent placement. At the time of approval, eptifibatide was approved for use at two doses, based on the PURSUIT trial (in patients with Acute Coronary Syndrome), and the IMPACT-II trial (in patients undergoing PCI). Despite this approval, the sponsor remained concerned about the level of inhibition of platelet activation (% IPA) achieved by these two regimens. In support of this possibility, data obtained in an earlier trial (PRIDE) suggested that there was a transient decrease in % IPA using the single-bolus dosing from PURSUIT and IMPACT-II and that this could be prevented by a second bolus of eptifibatide administered shortly after the first (see Pharmacokinetics review by Dr. Robbie). The ESPRIT trial was performed to obtain information about the clinical utility of this novel dosing regimen. A secondary aim of the study, also related to the level of anti-coagulation to be used, was to investigate the use of lower doses of heparin than the doses used in PURSUIT and IMPACT-II (and hence included in Integrilin labeling). The decreased heparin dose proposed for use results in a lowered target used for the level of anticoagulation during the PCI (reflected in the target activated clotting time, ACT). The impact of the use of less heparin following PCI has previously been studied for abciximab (Reopro), where it was associated with decreased bleeding (EPIC and EPILOGUE trials).

The second aspect of the planning for ESPRIT has to do with the potential ethics of conducting a placebo-controlled trial in patients undergoing PCI. At the time of the trial planning, there were three drugs approved for use in patients with acute coronary syndrome and patients undergoing PCI. These approvals were based on at least 9 placebo-controlled trials showing superiority of GPIIb/IIIa inhibitors relative to placebo in the prevention of clinically-significant endpoints including death and myocardial infarction. As a result, the FDA expressed some reservations about the ethics of exposing patients with ACS and those undergoing PCI to placebo (that is, not providing them active therapy), and the protocol was placed on Clinical Hold. Among other materials, the sponsor submitted information from investigators supporting the sponsor's contention that portions of the medical community remained uncertain about the necessity of the use of these agents in the setting of acute coronary syndrome/ PCI. In addition, the sponsor had included a provision for the use of 'bail-out' therapy with open-label GPIIb/IIIa inhibitors if the clinical situation warranted it in the ESPRIT trial. Following these discussions, the trial was allowed to go forward.

3.0 to 3.3 Materials Related to Approval Decision

3.1 Adequacy of Clinical Database

The clinical database submitted to the Agency included sufficient data regarding the clinical outcomes from the ESPRIT trial to adequately assess the safety and efficacy of eptifibatide in the population studied.

3.2 ESPRIT Trial Design

3.2.1 Title of Study

A Study of Integrilin (eptifibatide) in Patients Undergoing Non-Acute Percutaneous Coronary Intervention with Stent Implantation: Protocol 98-025.

3.2.2 Sites of Investigation and Investigators

The list of investigators and sites is found in section 16.1.4.4 of the electronic submission. This trial was conducted at 92 sites in the U.S. and Canada.

3.2.3 Study Background

Initial protocol submitted: 12.15.98

First protocol amendment:

This amendment clarified the adjudication process and the definitions of clinical endpoints. Section 8.1.1 was added to the protocol to clarify identification of events for adjudication by the CEC. In addition, the procedures for use of heparin were clarified.

Subject entry: 6.3.99 through early study termination (2.4.2000).

3.2.4 Study Design

This was a double-blind, multicenter, randomized, parallel-group, placebo-controlled trial in patients scheduled to undergo non-emergent percutaneous coronary intervention (PCI) with stent implantation. A total of approximately 2400 patients were randomized 1:1 to receive either eptifibatide or placebo. Study drug was initiated immediately before percutaneous coronary intervention (PCI) and was administered until hospital discharge or for a maximum of 18-24 hours. The eptifibatide dosing regimens used in this study were as follows:

Table 3.2.4.1 Dosing in ESPRIT[a].

Baseline Serum Crt	First Bolus (μg/kg)	Infusion (μg/kg/min)	Second Infusion[b] (μg/kg)
≤2.0 mg/dl	180	2.0	180
>2.0 and ≤4.0 mg/dl	180	1.0	180

a. From NDA 20-718, ESPRIT study report, table 9-1.
b. Administered 10 minutes after first bolus.
c. Initiated immediately after first bolus.

Concomitant Therapy

All patients received concomitant aspirin and heparin. Heparin was administered to attain an ACT of 200-300 seconds at the beginning of the procedure, and to maintain an ACT of >200 seconds throughout the procedure. Aspirin was administered to all patients unless there was a contraindication to its use.

If thrombolytics were indicated clinically, patients were first switched to open-label eptifibatide using the 'bail-out' kit (see below). If thrombolytics were still indicated, eptifibatide was discontinued.

Ticlopidine or clopidogrel were not permitted within 15 days before the PCI procedure except on the day of the procedure, when a loading dose of ticlopidine or clopidogrel was permitted before PCI. Adjunctive anti-platelet therapy with either ticlopidine 250 mg bid or clopidogrel 75 mg qd was encouraged following stent implantation.

Blinding

ESPRIT was a double-blind study. Study drug kits were provided to the participating sites containing four bolus injection vials and four infusion vials. The matching placebo was indistinguishable from eptifibatide.

Bail-Out Therapy

Treating physician could switch a patient to open-label eptifibatide therapy if they judged it to be in the best interests of the patient. To do this, study drug was stopped and the administrative center at Duke contacted for assignment of a 'bail-out' kit (containing placebo if the patient was in the eptifibatide group and eptifibatide if the patient was in the placebo group). Kits of both types had previously been provided to all sites. A bolus of study drug from a 'bail-out' kit was then administered, along with open-label eptifibatide infusion was to be started simultaneously at a dose of 1-2.0 μg/kg-min (depending on their serum creatinine). The infusion was to continue after 'bail-out' until discharge or up to a maximum of 18-24 hours, whichever occurred first.

3.2.5 Primary and Secondary Endpoints

Primary Endpoint

Incidence of death, myocardial infarction, urgent target vessel revascularization (UTVR), and need for 'bail-out' therapy within 48 hours.

Secondary endpoints

1) The composite of death, MI, and UTVR within 30 days.

2) The composite of death, MI, UTVR, and thrombotic 'bail-out' GP IIb/IIIa therapy within 12 and 24 hours, and 7 and 30 days.

3) The composite of death, MI and UTVR within 12, 24, and 48 hours and 7 Days.

4) The composite of death and MI within 24 and 48 hours, and 7 and 30 days.

Secondary endpoints (cont)

5)- The occurrence of any 'bail-out' GP IIb/IIIa therapy.

6)- The occurrence of thrombotic 'bail-out' GP IIb/IIIa therapy.

7)- The composite of death, MI, UTVR, and thrombotic 'bail-out' GP IIb/IIIa therapy as determined by the Principal Investigator within 24 and 48 hours, and 7 and 30 days.

8)- The composite of death, MI, and UTVR as determined by the Principal Investigator within 24 and 48 hours, and 7 and 30 days.

9)- The occurrence of post-PCI abrupt closure during the first 48 hours. If discharge occurred prior to 48 hours, this only included abrupt closure prior to discharge.

For each of the composite endpoints the endpoint was considered to have occurred at the time of the earliest event, regardless of the occurrence of later events.

Endpoint Definitions and Adjudication

With the exception of deaths, the primary and secondary endpoints all refer to adjudicated events, as opposed to events identified by the investigators. Certain events triggered central adjudication by the Central Events Classification Committee (CEC) (see Appendix One for list of individuals on committee). These events included:

- Ambiguous CK-MB (identified from core laboratory data analysis)
- Post-procedural abrupt closure identified on the case report form (CRF)
- MI identified on the CRF
- Repeat PCI identified on the CRF
- Coronary artery bypass grafting identified on the CRF

Definitions used during the adjudication process for the efficacy endpoints are summarized in the table below. Additional details of endpoint adjudication can be found in section 16.1.9.10.19 of the ESPRIT study report. If data submitted by investigator was ambiguous for any of the endpoints CEC personnel contacted site directly for additional information.

An MI could count as an event by meeting one of two criteria: enzymatic MIs, based on lab values from the core laboratory, and adjudicated MIs, identified by the investigators as MIs and then adjudicated centrally.

Table 3.2.5.1 Endpoint Definitions in ESPRIT[a].

Endpoint	Definitions
Enzymatic MI	Within 24 hours of PCI, two CK-MB values >3X above ULN[b]
Adjudicated MI	MI first identified by investigator and confirmed by CEC.
Adjudicated Urgent Target Vessel Revascularization	Identified by investigator and confirmed by CEC to be urgent[c] and occurring in the distribution of the initial PCI.
Adjudicated Thrombotic Bail-Out	Identified by through use of 'bail-out' therapy with GP IIb/IIIa inhibitor due to a thrombotic complication (e.g., abrupt closure, no reflow, visible thrombus). All other 'bail-out' usage was adjudicated as being non-thrombotic.

a. Data from ESPRIT study report, section 9.5.3.5.1.

b. With at least a 25% increase in CK-MB if the last pre-randomization value was above the upper limits of normal.

c. Urgent PCI must occur within 24 hours of onset of symptoms, defined as one or more episodes of rest pain, presumed to be ischemic in origin and lasting at least 5 minutes. Any CABG occurring within 24 hours of the initial PCI for unstable results was also considered urgent, even if ongoing ischemia was not present.

3.2.6 Inclusion/ Exclusion Criteria

Inclusion Criteria (must be present)

1. Have known coronary artery disease and be scheduled to undergo PCI with stent implantation.

2. Have received at least one dose (162 – 325 mg) of aspirin within 24 hours before the intervention (unless contraindicated).

3. Be willing and able to give informed consent.

4. Be a patient the Principal Investigator was not planning to treat with a GP IIb/IIIa inhibitor prior to initiation of intervention if the patient were not participating in this clinical trial.

Exclusion Criteria (cannot be present)

1. MI within the previous 24 hours before randomization.
2. Ongoing chest pain (or anginal equivalent) leading to urgent referral for PCI, or ongoing chest pain (or anginal equivalent) at the time of study randomization.
3. PCI of saphenous vein graft or internal mammary artery graft.
4. PCI within the previous 90 days before randomization.
5. Prior stent in target lesion.
6. Anticipated subsequent staged PCI for a period of 30 days after randomization.
7. Treatment with any parenteral or oral platelet GP IIb/IIIa inhibitor within the previous 30 days before study randomization.
8. Concurrent or anticipated treatment with any parenteral or oral platelet GP IIb/IIIa inhibitor or with warfarin for 30 days after study randomization.
9. Treatment with ticlopidine or clopidogrel within the previous 15 days before the PCI procedure, except for the day of PCI procedure.
10. History of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days of randomization.
11. History of a hemorrhagic stroke at any time, or stroke or TIA within 30 days of randomization.
12. Pregnancy. Premenopausal females should have had a negative pregnancy test confirmed before study enrollment.
13. Severe hypertension on therapy (SBP >200 mm Hg or DBP >110 mm Hg).
14. Major surgery within 6 weeks prior to randomization.
15. Known platelet count of $<100{,}000/mm^3$.
16. Participation in a study of experimental therapy within 30 days.
17. Renal dialysis within 30 days or a serum creatinine >4.0 mg/dL (350 µmol/L).
18. Known hypersensitivity to any component of the study drug.

3.2.7 Safety and Efficacy Endpoints Measured

The first table summarizes the timing of safety and efficacy assessments.

Table 3.1.7.1 Timetable for Clinical Observations and Lab Measurements in ESPRIT[a].

	Pre-Study	Prior to PCI[c]	Just Before PCI	During Infusion						
Visit Day:				10 min	6 Hrs	12 Hrs	18 Hrs	24 Hrs	48 Hrs or D/C	30 Days
Consent, Inclusion/Exclusion	X									
Medical History, Concom Meds	X									
12-lead ECG	X									
Serum Creatinine										
CK-MB	X	X			X	X	X	X		
Pregnancy Test	X									
Hgb/Hct, Platelet Count		X						X		
ACT[b]			X							
Treatment Assignment			X							
1st Study Drug Bolus			X							
2nd Study Drug Bolus				X						
Completion of CRF									X	X

a. Data from ESPRIT study report, table 9-6.
b. Activated Clotting Time to adjust heparin dose.
c. Within 4 hours of start of PCI.

Safety Measurements

Safety was assessed through the collection of bleeding complications, serious adverse events and laboratory data through the first 48 hours after initiation of study drug or to hospital discharge, whichever occurred first. Bleeding complications were assessed using the GUSTO and TIMI classifications (see Appendix Two for definitions used).

3.2.8 Statistical Considerations

Power

Sample size was determined using the endpoint of composite of death, MI, and UTVR within 30 days. Using the projected event rate of 11.0% for the placebo group, 1200 patients per treatment group had an 86% power to detect a 33% relative reduction (3.6% absolute reduction) in the percentage of patients with the composite endpoint within 30 days at the alpha=0.05 level.

Multiplicity

No adjustment for multiple comparisons was employed.

Interim Analyses

There were no planned interim analyses. There were, however, two interim efficacy analyses performed at the request of the Data Safety and Monitoring Committee, and the trial was stopped prematurely due to overwhelming efficacy. This decision is discussed thoroughly in the Statistical Review by James Hung, Ph.D., and the reader is referred to that document for details.

Statistical Analysis

1) Study Population

All analyses were per protocol and conducted on the 'all randomized' (intent-to-treat) population unless otherwise noted: all patients who received any study medication regardless of whether PCI or stenting was performed.

All but two patients had follow-up through 30 days. Neither of these individuals had a clinical event at the time they were lost to follow-up, and they were included in the denominator for all timepoints.

2) Efficacy Analyses

The primary statistical analysis was a chi-square test for the incidence of the primary endpoint. In addition, to adjust for various baseline and prognostic variables, a stratified Mantel-Haenszel tests was performed for the primary and key secondary composite endpoints and for those same composites later timepoints. The following covariates were included: age, gender, race, weight, history of hypertension, history of diabetes, history of hypercholesterolemia, cigarette smoking status, previous MI, previous PCI, previous CABG, previous stroke, history of peripheral vascular disease, primary reason for PCI/admission, use of unfractionated or low molecular weight heparin prior to entry into the catheterization laboratory, baseline CK, baseline CK-MB, baseline troponin, baseline serum creatinine, maximum procedural ACT.

Pharmacokinetics

No pharmacokinetic measurements or analyses were performed.

Safety

Safety analyses were descriptive in nature. See above for measured safety parameters.

3.3 Efficacy Outcomes for ESPRIT

3.3.1 Disposition of Subjects

Enrollment in ESPRIT is summarized below. Two individuals were lost to follow-up prior to 30 days.

Table 3.3.1.1 Subject enrollment and treatment in ESPRIT[a].

Population	Placebo N=1024	Eptifibatide N=1040
Total receiving any study drug	1024	1040
Use of bail-out therapy		
Received only study drug (i.e., no bail-out therapy)	981 (95.8%)	1005 (96.6%)
Bailed out to open-label eptifibatide	41 (4.0%)	35 (3.4%)
Bailed out to other GP IIb/IIIa inhibitor	2 (0.2%)	0 (0%)
Lost to follow-up prior to 30 days	1 (0.1%)	1 (0.1%)
Procedures		
Total receiving a stent	997 (97.4%)	986 (94.8%)
Total with PCI without a stent	18 (1.8%)	39 (3.8%)
Total who did not have PCI	9 (0.9%)	15 (1.4%)

a. Data from ESPRIT study report, table 10-1.

3.3.2 Subject Selection and Informed Consent

No information is available about subject selection in ESPRIT.

One site had issues arise regarding informed consent. Specifically, the angiographic substudy used intracoronary adenosine in the protocol (a non-approved indication). As such, a separate informed consent was to be used for this sub-study. At Beth Israel Hospital in Boston, no supplementary informed consent was obtained by the investigator until contacted by the sponsor. The investigator informed the IRB of his actions and contacted all patients to sign a supplemental informed consent. The FDA was contacted at the time of the discovery. The investigator was audited by COR and found otherwise to be in compliance with Good Clinical Practice. The angiographic substudy was not considered as part of the current review.

3.3.3 Protocol Deviations

The list of protocol deviations can be found in the table below. Both treatment groups had deviations detected in around 6% of the population. The following table details the small number of patients who were unblinded to study drug during ESPRIT along with the reasons for the unblinding. The small number of patients unblinded by the investigator is not sufficient to influence the outcome of the trial.

Table 3.3.3.1 Protocol Deviation in ESPRIT[a].

	Placebo N=1024	Eptifibatide N=1040
Inclusion Criteria	1 (0.1%)	1 (0.1%)
Exclusion Criteria	19 (1.9%)	15 (1.4%)
Discontinuation Failure[b]	0 (0%)	3 (0.3%)
Drug Dosing Error		
>20% Overdose	7 (0.7%)	8 (0.8%)
>20% Underdose	5 (0.5%)	7 (0.7%)
Use of prohibited concomitant meds	31 (3.0%)	24 (2.3%)

a. Data from ESPRIT study report, table 10.3.
b. Failure to discontinue medication during a serious bleeding event.

Table 3.3.3.2 Unblinding in ESPRIT[a].

Reasons for Unblinding	Placebo N=1024	Eptifibatide N=1040
Switch to other GPIIb/IIIa	1 (0.1%)	0 (0%)
Intracranial hemorrhage	0 (0%)	2 (0.2%)
Other serious bleeding event	1 (0.1%)	0 90%)
Other	5 (0.5)	5 (0.5%)
Total	7 (0.7%)	7 (0.7%)

a. Data from ESPRIT study report, table 10.4.

A potentially more serious breach of protocol relates to the disqualification of one of the principal investigators by his local Institutional Review Board.
at his institution 'as a result of problems in a clinical trial not related to ESPRIT.' The table in Appendix Four summarizes the results of an analysis eliminating from the ESPRIT study results. Excluding this site did not affect the primary results of the trial.

3.3.4 Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the subjects enrolled in ESPRIT are summarized below. The two treatment groups were well-balanced as regards to the standard patient demographics.

Table 3.3.4.1 Demographics from ESPRIT[a].

Baseline Characteristic	Placebo N = 1024	Eptifibatide N=1040
Age, years		
Mean (sd)	62±11	62±11
Age Group, n (%)		
< 65 years	580 (56.6%)	592 (56.9%)
65 - 74 years	308 (30.1%)	292 (28.1%)
≥ 75 years	136 (13.3%)	156 (15.0%)
Gender, n (%)		
Male	742 (72.5%)	760 (73.1%)
Female	282 (27.5%)	280 (26.9%)
Race, n (%)		
White	930 (90.8%)	927 (89.1%)
Black	43 (4.2%)	52 (5.0%)
Hispanic	21 (2.1%)	21 (2.0%)
Asian	11 (1.1%)	16 (1.5%)
Other	19 (1.8%)	43 (4.1%)
Weight, kg		
Mean (sd)	86.6±18	85.1±18
Enrollment by Nation		
U.S.	759 (74.1%)	772 (74.2%)
Canada	265 (25.9%)	268 (25.8%)

a. Data from ESPRIT study report, table 14.1.4 and at request of reviewer.

Table 3.3.4.2 Past Medical History in ESPRIT[a].

Baseline Characteristic	Placebo N = 1024	Eptifibatide N=1040
Cardiovascular Hx		
Previous MI	321 (31.3%)	331 (31.8%)
Previous PCI	246 (24.0%)	237 (22.8%)
Previous CABG	105 (10.3%	106 (10.2%)
Previous Stroke	45 (4.4%)	44 (4.2%)
Peripheral Vascular Disease	71 (6.9%)	66 (6.3%)
Other Medical History		
Hypertension	605 (59.1%)	608 (58.5%)
Diabetes	211 (20.6%)	208 (20.0%)
Hypercholesterolemia	599 (58.6%)	600 (57.7%)
Cigarette Smoker	702 (69.3%)	748 (72.4%)

a. Data from ESPRIT study report, table 11-2 and 11-3.

3.3.4 Subject Demographics & Baseline Characteristics (cont)

Table 3.3.4.3 Reasons for Admission in ESPRIT[a].

Reason for Admission	Placebo N=1024	Eptifibatide N=1040
Positive functional study only	91 (8.9%)	96 (9.2%)
Other anginal equivalent	24 (2.3%)	23 (2.2%)
Stable angina	387 (37.8%)	407 (39.1%)
Unstable angina/NQWMI[b]		
<48 hours	140 (13.7%)	139 (13.4%)
48 hours to 6 months	333 (32.5%)	331 (31.8%)
Acute MI with ST-T elevation within 7 days	49 (4.8%)	44 (4.2%)

a. Data from ESPRIT study report, table 11-4.
b. Non-Q-Wave MI.

Table 3.3.4.4 Angiographic Findings At Baseline in ESPRIT[a].

	Placebo	Eptifibatide
% Stenosis of Index Lesion	N=1016 87±9%	N=1034 87±9%
TIMI Grade Flow at baseline	N=962	N=995
0	47 (4.9%)	34 (3.4%)
1	22 (2.3%)	33 (3.3%)
2	89 (9.3%)	86 (8.6%)
3	804 (83.6%)	842 (84.6%)
Target Vessel	N=1022	N=1039
LAD	396 (38.7%)	404 (38.9%)
RCA	344 (33.7%)	364 (35.0%)
LCX[b]	275 (26.9%)	265 (25.5%)
Left Main	7 (0.7%)	6 (0.6%)
Thrombus present in index lesion at baseline	N=984 41 (4.2%)	N=1011 47 (4.6%)

a. Data from ESPRIT study report, table 11-4.
b. Left Circumflex.

3.3.5 Concomitant Therapies

Concomitant Medications

Use of other concomitant anti-platelet therapy was common on the day of and within 48 hours of PCI. Use of ticlopidine was rare, as was the use of stenting without the use of either ticlopidine or clopidogrel. Use of heparin after PCI was also uncommon.

Table 3.3.5.1 Concomitant Anti-Platelet Therapy[a].

	Placebo N=1024	Eptifibatide N=1040
Aspirin	1021 (99.7%)	2056 (99.7%)
Ticlopidine	27 (2.6%)	28 (2.7%)
Clopidogrel	982 (95.9%)	991 (95.4%)
Heparin[c]	62 (1.6%)	53 (5.1%)
Neither Ticlopidine Nor Clopidogrel	18 (1.7%)	30 (2.9%)

a. Data from ESPRIT study report, table 11-5 and from sponsor at reviewer's request.
b. Refers to the use of the drugs on the day of PCI or within 48 hours.
c. Refers to the use of heparin within 48 hours after PCI.

Heparin use prior to the PCI was also balanced between placebo (27.6%) and eptifibatide (28.3%). The amount of heparin used during PCI was also balanced, as judged by the mean maximal ACT and the total heparin bolus administered during PCI (data not shown).

Concomitant Stent Use

The use of stents was required for entry into the trial, but the type to be used was left to local practice. The treatment groups were overall balanced in regard to the number and type of stents used, as shown in the two tables below. The first table summarizes the number of stents received in each treatment group, followed by a summary of the most common type of stents.

Table 3.3.5.2 Number of Stents Received in ESPRIT[a].

	Placebo N=1024	Eptifibatide N=1040
Total Number of Lesions Tx'd	1389	1394
Treated lesions receiving stents	1262 (90.9%)	1234 (88.5%)
Number of Stents Received		
None	27 (2.6%)	51 (5.2%)
One	650 (63.5%)	676 (65.0%)
Two	242 (23.6%)	231 (22.5%)
Three	90 (8.8%)	51 (5.2%)
Four or More	15 (1.5%)	19 (2.1%)

a. Data from sponsor at reviewer's request.

The types of stents used were balanced between the treatment groups. None of the patients received the Palmaz-Schatz or Wiktor stents.

Table 3.3.5.3 Types of Stents Used in ESPRIT[a].

	Placebo N=1024	Eptifibatide N=1040
DUET	250 (25.1%)	229 (23.2%)
NIR	185 (18.6%)	190 (19.3%)
gfx	119 (11.9%)	120 (12.2%)
MULTI-LINK	70 (7.0%)	68 (6.9%)
Cross-Flex	69 (6.9%)	53 (5.4%)
NIR PRIMO	50 (5.0%)	38 (3.9%)
Biodivisio	41 (4.1%)	43 (4.4%)
NIR Royale	38 (3.8%)	35 (3.5%)
gfx2	29 (2.9%)	32 (3.2%)
S540	24 (2.4%)	24 (2.4%)
NIR on Ranger	18 (1.8%)	26 (2.6%)
Other stent types	48 (4.8%)	37 (3.7%)

a. Data from sponsor at reviewer's request.

Use of other cardiac procedures

The use of rotablator devices, intracoronary thrombolytics or thrombectomy was rare in the ESPRIT trial (2.3% for rotablator, <0.1% for thrombolytics and thrombectomy). Balloon expansion of the intracoronary lesion was done in 81.7% of the placebo and 81.3% of the eptifibatide groups.

3.3.6 Extent of Exposure to Study Drug in ESPRIT

The extent of exposure to study drug was well-balanced, as summarized in the table below.

Table 3.3.6.1 Exposure to Study Drug in ESPRIT[a].

Study Drug Infusion Duration (hours)	Placebo (N = 1024)	Eptifibatide (N = 1040)
0 to <3	58 (5.7%)	71 (6.9%)
3 to <6	14 (1.4%)	17 (1.6%)
6 to <12	9 (0.9%)	15 (1.4%)
12 to <18	163 (16.0%)	170 (16.4%)
18 to <24	720 (70.5%)	711 (68.6%)
≥24	57 (5.6%)	52 (5.0%)
Mean	18.0	17.7
Median	18.4	18.3

a. Data from ESPRIT study report, table 12-1.

Forty-one (4.0%) of placebo and 35 (3.4%) of eptifibatide-treated patients received 'bail-out' therapy. Two (0.2%) patients randomized to the placebo group were switched to an open label GP IIb/IIIa inhibitor other than eptifibatide. Use of bail-out therapy is discussed further in the Endpoints sections below.

3.3.7 Primary Efficacy Analyses of ESPRIT

The ESPRIT study was halted prematurely by the DSMC for 'overwhelming treatment difference on the efficacy endpoints.' Because of slower than expected patient accrual, on December 16, 1999 the DSMC asked the Duke Clinical Research Institute (DCRI) to conduct an interim efficacy analysis. As a result of this analysis, a second interim analysis was requested that resulted in halting the trial. Details of the meetings and the interim analyses can be found in the statistical review by James Hung, Ph.D. The incidence of the primary endpoint at the second interim analysis, that formed the basis for the decision to halt the trial, is shown (shaded) below, along with its components.

Table 3.3.7.1 Efficacy Endpoints At the Time of the Second Interim Analysis from ESPRIT[a].

48-Hour Endpoint	Treatment A N=879	Treatment B N=879	p-Value
Death/MI/UTVR/TBO	55 (6.3%)	90 (10.2%)	0.0024
Death/MI	43 (4.9%)	76 (8.6%)	0.0017
Death	0[b]	2 (0.2%)	0.16
MI	43 (4.9%)	74 (8.4%)	0.0030
UTVR	5 (0.6%)	6 (0.7%)	0.76
TBO	10 (1.1%)	19 (2.2%)	0.092

a. Data from draft statistical review by James Hung, Ph.D., table 3a.
b. Unlikely to be correct, as a death had previously been reported in the 1st interim analysis.

The final dataset included data from 2,064 patients (out of the 2,400 planned for enrollment). The primary efficacy analysis was the composite of death, MI, urgent target vessel revascularization (UTVR) and the use of 'bail-out' therapy (TBO at 48 hours.

Table 3.3.7.2 Primary Endpoint and Its Components from ESPRIT[a,b].

48-Hour Endpoint	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk (95% C.I.) p-Value
Death/MI/UTVR/TBO	108 (10.5%)	69 (6.6%)	37%/3.9%	0.63 (0.47, 0.84) 0.0015
Death	2 (0.2%)	1 (0.1%)	51%/ 0.1%	0.49 (0.04, 5.42) 0.55
MI	92 (9.0%)	56 (5.4%)	40%/ 3.6%	0.60 (0.22, 1.62) 0.0015
UTVR	10 (1.0%)	6 (0.6%)	41%/ 0.4%	0.60 (0.22, 1.62) 0.30
TBO	22 (2.1%)	10 (1.0%)	55%/ 1.2%	0.45 (0.22, 0.94) 0.029

a. Data from ESPRIT study report, table 11-5.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

3.3.8 Additional Efficacy Analyses from ESPRIT

The sponsor analyzed a variety of secondary endpoints at timepoints between 12 hours and 30 days after initiation of therapy. Several of these results are summarized in the tables below. The reduced risk for relevant clinical endpoints remained stable through 30 days.

Table 3.3.8.1 Secondary Endpoints in ESPRIT: Death/MI/UTVR/TBO through 30 Days[a,b].

30 Day Timepoint: Death/MI/UTVR/TBO	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk p-Value
12 Hours	65 (6.3%)	37 (3.6%)	44%/ 2.8%	0.56, 0.0035
24 Hours	105 (10.3%)	69 (6.6%)	35%/ 3.6%	0.65, 0.0031
48 Hours (Primary Endpt)	108 (10.5%)	69 (10.5%)	37%/ 3.6%	0.63, 0.0015
7 Days	114 (11.1%)	75 (7.5%)	35%/ 3.9%	0.65, 0.0020
30 Days	120 (11.7%)	78 (7.5%)	36%/ 4.2%	0.64, 0.0011

a. Data from ESPRIT study report, table 11-8.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

Table 3.3.8.2 Secondary Endpoints in ESPRIT: Death/MI through 30 Days[a,b].

30 Day Timepoint: Death/MI	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk p-Value
24 Hours	91 (8.9%)	57 (5.5%)	38%/ 3.4%	0.62, 0.0027
48 Hours	94 (9.2%)	57 (5.5%)	40%/ 3.7%)	0.60 0.0013
7 Days	99 (9.7%)	63 (6.3%)	38%/ 3.8%	0.63 0.0023
30 Days	104 (10.2%)	66 (6.3%)	38%/ 3.8%	0.62 0.0016

a. Data from ESPRIT study report, table 11-13.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

In data not shown, the sponsor performed a time-to-event analysis for the endpoint of Death/ MI/ Urgent revascularization. As expected from the categorical tables above, >90% of the events had occurred by the end of 48 hours after PCI.

The sponsor analyzed the occurrence of death and/or 'large MIs' (defined as at least one CK-MB value ≥5 times ULN). Approximately 50% of the MIs in ESPRIT were classified as 'large' using this definition. No ECGs were obtained at 30 days, so the definition used does not include MIs detected through changes in the ECG (*e.g.*, appearance of Q-waves).

Table 3.3.8.3 Secondary Endpoints in ESPRIT: Death and/or 'Large MI' through 30 Days[a,b].

Death and/or Large MI at 30 days	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	p-Value
30 Days	56 (5.5%)	38 (3.7%)	33%/ 1.8%	0.048

a. Data from ESPRIT study report, table 11-13.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

The incidence of bail-out to open-label therapy was measured separately from the primary endpoint, where bail-out (TBO) was a component. Bail-out could occur because of thrombotic complications (*e.g.*, abrupt closure of vessel, no reflow, visible thrombus) or for other reasons (*e.g.*, suboptimal dilatation of vessel). Very few patients had 'bail-out'; of these, bail-out was more common in the placebo group.

Table 3.3.8.4 Secondary Endpoints in ESPRIT: Need for Bail-Out Therapy[a].

	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk, p-Value
Bail-Out for Any Reason	43 (4.2%)	35 (3.4%)	20%/ 0.8%	0.80, 0.321
Bail-Out for Non-Thrombotic Reasons	21 (2.1%)	25 (2.5%)	--	--
Bail-Out for Thrombotic Reasons	22 (2.1%)	10 (1.0%)	55%/ 1.2%	0.45, 0.029

a. Data from ESPRIT study report, table 11-13. Statistics per sponsor.

3.3.9 Investigator-Derived Endpoints in ESPRIT

The pre-specified primary endpoint was based on the centrally-adjudicated clinical events. Similar to what was done in the earlier PURSUIT trial, the sponsor also analyzed information on the occurrence of clinical events as designated by the investigators. In this analysis, eptifibatide use was associated with a decreased number of clinical events that did not achieve nominal statistical significance. This outcome was related to both fewer events than the centrally-adjudicated endpoints and to a smaller difference between placebo and eptifibatide. For example, at 48 hours there was a 37% reduction in the incidence of Death/MI/UTVR/TBO as determined by the CEC compared with 22% reduction in the same endpoint as assessed by investigators.

Table 3.3.9.1 Death/MI/UTVR/TBO Assessed by Investigators[a,b].

Death/MI/UTVR/TBO	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk p-Value
24 Hours	56 (5.5%)	50 (4.8%)	12%/ 0.7%	0.87, 0.496
48 Hours	64 (6.3%)	51 (4.9%)	22%/ 1.3%	0.78, 0.185
7 Days	71 (6.9%)	57 (5.5%)	21%/ 1.5%	0.80, 0.171
30 Days	77 (7.5%)	60 (5.8%)	23%/ 1.8%	0.77, 0.110

a. Data from ESPRIT study report, table 11-15.
b. All events as clinical events designated by the investigators on CRF.

In ESPRIT, the investigators didn't have access to the centrally-measured CK-MB results, collected every 8 hours for the first twenty-four hours after PCI. As such, MIs would have been diagnosed based on separate samples submitted to the local labs, ordered by the investigators on the basis of clinical symptoms and ECGs. As a result, the number of events reported by the investigators at any time is fewer in this table when compared with the centrally-adjudicated results (see above). The results for the Death/MI endpoint as designated by the investigators are summarized below.

Table 3.3.9.2 Secondary Endpoints in ESPRIT: Death/MI Assessed by Investigators[a,b].

Death/MI	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute	Relative Risk p-Value
24 Hours	36 (3.5%)	35 (3.4%)	3%/ 0.1%	0.96, 0.852
48 Hours	45 (4.4%)	37 (3.6%)	18%/0.8%	0.803, 0.330
7 Days	52 (5.1%)	42 (4.0%)	22%/ 1.1%	0.787, 0.257
30 Days	59 (5.8%)	44 (4.2%)	28%/ 1.6%	0.723, 0.110

a. Data from ESPRIT study report, table 11-16. Statistics per sponsor.
b. All events as clinical events designated by the investigators on CRF.

Finally, the agreement between the investigators and the CEC was analyzed in the table below. Investigators identified 20 events that were considered non-events by the CEC. Overall, the CEC added 88 MIs not designated as such by the investigators, while the CEC removed 20 events identified as MIs by the investigators.

Table 3.3.9.3 MIs at 48 Hours According to CEC and Investigator Designation[a].

	CEC Yes	CEC No	Total Per the PI
Investigator Yes	60	20	80
Investigator No	88	1896	1984
Total Events Per the CEC	148	1916	2064

a. Data from ESPRIT study report, table 11-16.

It is of interest that the majority of the MIs added by the CEC were in the placebo group. The table below summarizes the MIs at 48 hours per the CEC and per the investigators.

3.3.9 Investigator-Derived Endpoints in ESPRIT (cont)

Table 3.3.9.4 Exploratory Analysis in ESPRIT: MIs Assessed by Investigators and CEC[a,b].

	Placebo N=1024	Eptifibatide N=1040
MIs Per CEC at 48 Hours	92 (9.0%)	56 (5.4%)
MIs Per Investigators at 48 Hours	44 (4.3%)	36 (3.5%)
Number of MIs Added by CEC	46 (50% of total)	20 (36% of total)

a. Data from ESPRIT study report, table 11-16. Statistics per sponsor.
b. All events as clinical events designated by the investigators on CRF.

Discordance between the CEC- and investigator-derived endpoints was also seen in the PURSUIT trial. In PURSUIT, similar to ESPRIT, certain clinical events triggered a review of the event by the CEC. Like ESPRIT, the number of MIs detected centrally was considerably larger than the number detected by the investigators. In PURSUIT, the incidence of Death/MI after 30 days, adjudicated by the CEC, was the primary endpoint. In contrast with ESPRIT, the results were more robust statistically for the investigator-derived endpoints.

Table 3.3.9.5 Clinical Events in PURSUIT Trial[a].

	Placebo N=4739	Eptifibatide 180/2.0 N=4722	Eptifibatide 180/1.3 N=1487	p-Value
Death/MI at 30 Days				
CEC Adjudicated Event	745 (15.7%)	672 (14.2%)	200 (13.4%)	0.042[b] 0.038[c]
Investigator Designated Event	475 (10.0%)	380 (8.0%)	128 (8.6%)	0.001[b] 0.003[c]
MI				
CEC Adjudicated Event	568 (	507 (	150 (	NA
Investigator Designated Event	298	215	78	NA

a. Data from primary Medical Review by Isaac Hammond, dated 2.17.98.
b. Comparison of placebo with 1880/2.0 group.
c. Comparison of all three groups.

3.3.10 Sub-Group Analyses of Efficacy from ESPRIT

The sponsor analyzed the results based on a variety of demographics and clinical characteristics of the patients entering the trial. These are summarized in the tables below. Overall, the effect of eptifibatide to reduce the incidence of the primary endpoint extended across all sub-groups with data summarized below.

Table 3.3.10.1 Primary Endpoint by Demographic Characteristics[a,b].

Demographic	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute
Age			
<65 Years	47/580 (8.1%)	40/592 (6.8%)	17%/ 1.3%
≥65 Years	61/444 (13.7%)	29/448 (6.5)	53%/ 7.3%
Gender			
Male	67/742 (9.0%)	52/760 (6.8%	24%/ 2.2%
Female	41/282 (14.5)	17/280 (6.1%)	58%/ 8.5%
Race			
White	97/930 (10.4%)	61/927 (6.6%)	37%/ 3.8%
Non-White	11/94 (11.7%)	8/113 (7.1%)	40%/ 4.6%

a. Data from ESPRIT study report, table 11-22. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

3.3.10 Sub-Group Analyses of Efficacy from ESPRIT (cont)

Table 3.3.10.2 Primary Endpoint by Reason for Admission[a,b].

Reason for Admission	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute
Stable Angina	28/387 (7.2%)	22/407 (5.4%)	25%/ 1.8%
Unstable Angina			
<48 Hours	21/140 (15.0%)	11/139 (7.9%)	47%/ 7.1%
48 Hours to 6 Months	37/333 (11.1%)	19/331 (5.7%)	48%/ 5.4%
Acute ST-Segment Elevation in past 7 Days	10/49 (20.4%)	5/44 (11.4%)	44%/ 9.0%
Positive Function Test	10/91 (11.0%)	8/96 (8.3%)	24%/ 2.7%
Other Anginal Equivalent	2/24 (8.3%)	4/23 (17.4%)	-109%/ -9.1%

a. Data from ESPRIT study report, table 11-23. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

The protocol recommended the use of heparin with a goal of an ACT between 200 and 300 seconds, subject to local practice. The next table summarizes the results according to the target ACT.

Table 3.3.10.3 Primary Endpoint by Degree of Anti-Coagulation During PCI[a,b].

ACT	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute
<200 secs	4/40 (10.0%)	2/37 (5.4%)	46%/ 4.6%
200 to 300 secs	73/705 (10.4%)	45/654 (6.9%)	34%/ 3.5%
>300 secs	29/254 (11.4%)	22/325 (6.8%)	41%/ 4.6%

a. Data from ESPRIT study report, table 11-24. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

The protocol did not specify the type of stent to be used by the investigators. Recall that the type of stent used was balanced between the two treatment groups. The incidence of the primary endpoint according to the use of the more common stent types is shown below. The trend towards a favorable effect of eptifibatide on the primary endpoint is evident for each type of stent.

Table 3.3.10.4 Incidence of Primary Endpoint by Stent Use[a,b].

Stent Type	Placebo	Eptifibatide	% Reduction Relative/Absolute
DUET (n=479)	29/250 (11.6%)	18/229 (7.9%)	32%/ 3.7%
NIR (n=375)	24/185 (13.0%)	10/190 (5.3%)	59%/ 7.7%
gfx (n=239)	13/119 (10.9%)	11/120 (9.2%)	16%/ 1.8%
MULTI-LINK (n=138)	6/70 (8.6%)	4/68 (5.9%)	31%/ 2.7%
Cross-Flex (n=122)	8/69 (11.6%)	2/53 (3.8%)	67%/ 7.8%

a. Data from sponsor at reviewer's request. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

Finally, the sponsor analyzed the primary endpoint according to the presence of several clinical characteristics at baseline. These analyses are summarized in the tables below.

3.3.10 Sub-Group Analyses of Efficacy from ESPRIT (cont)

Table 3.3.10.5 Primary Endpoint by Cardiovascular Risk Factors[a,b].

Risk Factor at Baseline	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute
Diabetes			
Diabetic	14/211 (6.6%)	8/208 (3.8%)	42%/ 2.8%
Non-Diabetic	94/813 (11.6%)	61/832 (7.3%)	37%/ 4.2%
Smoker			
Current Smoker	42/228 (10.5%	14/250 (5.6%)	47%/ 4.9%
Former Smoker	46/474 (9.7%)	38/498 (7.6%)	21%/ 2.1%
Non-Smoker	36/311 (11.6%)	17/285 (6.0%)	48%/ 5.6%
Hypertension			
Hypertensive	65/605 (10.7%)	43/608 (7.1%)	34%/ 3.7%
Non-Hypertensive	43/418 (10.3%)	26/432 (6.0%)	41%/ 4.3%
Lipid			
Hyperlipidemic	57/599 (9.5%)	36/600 (6.0%)	37%/ 3.5%
Non-Hyperlipidemic	51/424 (12.0%)	33/440 (7.5%)	38%/ 4.5%

a. Data from ESPRIT study report, table 11-25. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

Table 3.3.10.6 Primary Endpoint by Cardiovascular Disease[a,b].

Risk Factor at Baseline	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/Absolute
Myocardial Infarction			
Yes	33/321 (10.3%)	26/331 (7.9%)	24%/ 2.4%
No	75/703 (10.7%)	43/709 (6.1%)	43%/ 4.6%
Previous PCI			
Yes	30/246 (12.5%)	23/237 (9.7%)	20%/ 2.5%
No	78/778 (10.0%	46/803 (5.7%)	43%/ 4.3%
Previous CABG			
Yes	9/105 (8.6%)	5/106 (4.7%)	45%/ 3.9%
No	99/919 (10.8%)	64/934 (6.9%)	36%/ 3.9%
Hx of Peripheral Vasc Dis			
Yes	7/71 (9.9%)	4/66 (6.1%)	39%/ 3.8%
No	101/953 (10.6%)	65/974 (6.7%)	37%/ 3.9%
Hx of Stroke			
Yes	3/45 (6.7%)	1/44 (2.3%)	66%/ 4.4%
No	105/979 (10.7%)	68/996 (6.8%)	36%/ 3.9%

a. Data from ESPRIT study report, table 11-26. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

Finally, the sponsor analyzed the results arranged by country where the study was performed. Looking at the center that enrolled at least 50 patients, eptifibatide reduced the incidence of the primary endpoint in both countries.

Table 3.3.10.7 Primary Endpoint by Country Disease (Canada vs. U.S.)[a,b].

Study Country	Placebo N=759 (U.S.) 265 (Canada)	Eptifibatide N=772 (U.S.) 268 (Canada)	Odds Ratio p-Value
U.S.	89 (11.7%)	56 (7.3%)	0.59, 0.0028
Canada	19 (7.2%)	13 (4.9%)	0.66, 0.26

a. Data from FDA statistical review by Jim Hung. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.
b. All events as adjudicated by the Central Events Classification Committee (CEC).

3.4 Safety Outcomes from ESPRIT

The sponsor points out that there are four populations in the ESPRIT study, based on their initial randomization and whether or not they received bail-out therapy: 1) patients randomized to placebo who did not receive 'bail-out' therapy, 2) patients randomized to eptifibatide who did not receive 'bail-out' therapy, 3) patients randomized to placebo who were bailed out, and 4) patients randomized to eptifibatide who were bailed out. The sponsor used these four groups to report bleeding adverse events. For other AEs, the sponsor used 'as-randomized' populations (that is, all patients randomized to placebo, even those who received 'bail-out' eptifibatide, were counted as placebo). Since more bail-outs occurred with the placebo group, and the bail-out group is 'sicker' than the group who were not 'bailed-out,' this has the effect of increasing slightly the number of adverse events ascribed to the placebo group. The practical consequences of this are limited: by any usual metrics, the use of eptifibatide was associated with more bleeding than placebo.

3.4.1 Defined Safety Endpoints Collected In ESPRIT

In ESPRIT, safety was assessed by an evaluation of bleeding complications, serious non-bleeding adverse events, and laboratory data (hemoglobin, hematocrit and platelet count) collected through 48 hours or hospital discharge. Mortality and hospitalizations through 30 days were also collected. A comparison of the bleeding events reported in the major trials of GPIIb/IIIa inhibitors can be found in Appendix Four. Of particular interest is the consistent pattern of decreased bleeding in those trials that utilized a lower dose of heparin during PCI.

3.4.2 Comments on Specific Safety Parameters

Deaths and Serious Adverse Events

The first table below summarizes the occurrence of deaths and serious adverse events in the first 30 days after randomization. The narratives from the 10 deaths were reviewed; bleeding adverse events were common in both treatment groups, and deaths were related to underlying cardiovascular disease.

Table 3.4.2.1 Adverse Experiences Reported in ESPRIT[a].

Event, total (% of subjects)	Placebo N = 1024	Eptifibatide N=1040
Death[b]	6 (0.6%)	4 (0.4%)
SAE[b]	71 (6.9%)	100 (9.6%)
Discontinuations due to AE	20 (2.%)	60 (5.8%)

a. Data from ESPRIT study report, table 12-19.
b. Deaths and SAEs reported within 30 days of randomization.

Of the SAEs reported, bleeding SAEs predominated, and will be discussed separately as part of the Adverse Events. Strokes, including intracranial hemorrhage, occurred rarely in the trial, as summarized below.

Table 3.4.2.2 Strokes During ESPRIT[a].

Strokes During Hospitalization	Placebo (N = 1024)	Eptifibatide (N = 1040)
All Reported Strokes	1 (0.1%)	3 (0.3%)
Primary hemorrhagic	1 (0.1%)	2 (0.2%)
Cerebral infarction	0 (0.0%)	1 (0.1%)
Infarction with hemorrhagic conversion	0 (0.0%)	0 (0.0%)

a. Data from ESPRIT study report, table 12-23. All events adjudicated by the CEC.

Bleeding Adverse Events

Of the adverse events reported in ESPRIT, bleeding AEs predominated. These were captured in two ways: through spontaneous reporting and through analysis of the laboratory data through 48 hours or hospital discharge. Both types of adverse events were more common in the group receiving eptifibatide. The first two tables summarize the bleeding adverse events categorized per the TIMI classification. In data not summarized, there was no clear association between increasing dose of heparin and risk of bleeding (ESPRIT study appendix 14.3.8).

Table 3.4.2.3 Bleeding Adverse Events in ESPRIT using TIMI Classification[a].

Bleeding Severity (TIMI Criteria)[b]	Placebo (N = 1024)	Eptifibatide (N =1040)
Major	4 (0.4%)	13 (1.3%)
Minor	18 (2.0%)	29 (3.0%)
Hemoglobin/Hematocrit drop with no bleeding site identified	6 (0.7%)	0 (0.0%)
Insignificant	81 (8.8%)	197 (20.3%)
None	813 (88.2%)	733 (75.4%)
Unresolved	102	68

a. Data from ESPRIT study report, table 12-3.
b. Definitions can be found in Appendix Two (definitions).

These results do not change materially when the patients who received bail-out therapy were analyzed separately.

Table 3.4.2.4 Bleeding Adverse Events Grouped by Use of Bail-out and TIMI Classification[a].

Bleeding Severity (TIMI criteria)[b]	Placebo (N =981)	Eptifibatide (N =1005)	Placebo With Bail-out (N =41)	Eptifibatide with Bail-out (N =35)
Major	4 (0.5%)	11 (1.2%)	0 (0%)	2 (5.9%)
Minor	12 (1.4%)	26 (2.8%)	5 (12.8%)	3 (8.8%)
Hemoglobin/Hematocrit drop with no bleeding site identified	6 (0.7%)	0 (0.0%)	0 (0%)	0 (0%)
Insignificant	73 (8.3%)	188 (20.0%)	8 (20.5%)	9 (26.5%)
None	786 (89.2%)	713 (76.0%)	26 (66.7%)	20 (58.8%)
Unresolved	100 (10.2%)	67 (6.8%)	2	1

a. Data from ESPRIT study report, table 12-4.
b. Definitions can be found in Appendix Two (definitions).

Similarly, bleeding events were more common when bleeding was analyzed using the GUSTO criteria. In data not shown, the need for transfusion of RBCs or platelets was similar in the two treatment groups (see ESPRIT study report, appendix table 14.3.5 for details).

Table 3.4.2.5 Bleeding Adverse Events Grouped by GUSTO Classification[a].

Maximum Severity of Any Bleeding Event (GUSTO)[b]	Placebo (N=1024)	Eptifibatide (N=1040)
Severe or life-threatening	5 (0.5%)	7 (0.7%)
Moderate	11 (1.1%)	14 (1.3%)
Mild	95 (9.3%)	228 (21.9%)
None	913 (89.2%)	791 (76.1%)

a. Data from ESPRIT study report, table 12-7.
b. Definitions can be found in Appendix Two (definitions).

Identified bleeding sites are summarized below. Note that despite their rarity, severe/ life-threatening (retroperitoneal or intracranial) bleeding was reported more commonly with eptifibatide use.

Table 3.4.2.6 Identified Sites of Bleeding in ESPRIT[a].

	Placebo (N = 1024)	Eptifibatide (N = 1040)
TIMI Major bleeding	4	13
Access site	1(0.1%)	8 (0.8%)
Intracranial	1 (0.1%)	2 (0.2%)
Hematuria	0 (0%)	1 (0.1%)
Hematemesis	0 (0%)	1 (0.1%)
Respiratory	0 (0%)	0 (0%)
Retroperitoneal	0 (0%)	3 (0.3%)

a. Data from ESPRIT study report, table 12-6.

Table 3.4.2.6 Identified Sites of Bleeding in ESPRIT[a] (cont).

	Placebo (N = 1024)	Eptifibatide (N = 1040)
TIMI Minor bleeding	18	29
Access site	8 (0.9%)	10 (1.0%)
Hematuria	8 (0.9%)	14 (1.4%)
Hematemesis	4 (0.4%)	6 (0.6%)
Respiratory	0 (0%)	0 (0%)
Retroperitoneal	0 (0%)	0 (0%)

a. Data from ESPRIT study report, table 12-6.

The sponsor performed a series of exploratory analyses to examine the interaction between eptifibatide and other drugs (thienopyridines, ASA, heparin, low-molecular-weight heparin) and between other demographics related to the PCI (*e.g.*, methods used for hemostasis). Taken in total, these analyses suggest that the combined use of eptifibatide and other products and procedures that affect hemostasis does increase the risk of major and minor bleeding, with odds ratios of between 1.5 and 4 for most analyses. No class of drugs or procedure has a particularly large effect relative to the group, however. See ESPRIT study report appendix tables 14.3.8 to 14.3.50 for details.

Thrombocytopenia

Eptifibatide use has been associated with thrombocytopenia, and the sponsor summarized its occurrence in ESPRIT. Both cases of profound thrombocytopenia and an overall excess of cases of all severities were seen in the eptifibatide group.

Table 3.4.2.7 Nadir Platelet Count Through 48 Hours in ESPRIT[a].

Nadir Platelet Count (per mm^3)	Placebo (N = 1024)	Eptifibatide (N = 1040)
<20,000	0 (0.0%)	2 (0.2%)
20,000 to <50,000	0 (0.0%)	0 (0.0%)
50,000 to <100,000	4 (0.4%)	7 (0.7%)
≥100,000	954 (93.2%)	980 (94.2%)
≤100,000 or ≥50% decrease from baseline	6 (0.6%)	12 (1.2%)
Missing	66 (6.4%)	51 (4.9%)

a. Data from ESPRIT study report, table 12-26.

Discontinuations

The next table summarizes the discontinuations during the double-blind portion of the study. Early terminations for bleeding AEs are prominently more common in the eptifibatide group.

Table 3.4.2.8 Discontinuations in ESPRIT[a].

Discontinuations	Placebo N=1024	Eptifibatide N=1040
Early Termination Per Study Design		
Patients Discharged	73 (7.1%)	57 (5.5%)
'Bail-out' to open-label eptifibatide	40 (3.9%)	34 (3.3%)
'Bail-out' to other GPIIb/IIIa's	2 (0.2%)	0 (0%)
Total Terminations 'Per Study'	115 (1.2%)	91 (8.8%)
Early Termination Not Per Study Design		
Bleeding Adverse Events	9 (0.9%)	48 (4.6%)
Non-Bleeding Adverse Events	11 (1.1%)	12 (1.2%)
Consent Withdrawn	4 (0.4%)	5 (0.5%)
Death	0 (0%)	1 (0.1%)
Need for CABG	4 (0.4%)	6 (0.6%)
Unable to Perform PCI	8 (0.8%)	8 (0.8%)
IV Line Placement	4 (0.4%)	7 (0.7%)
Other Reason	61 (6.0%)	58 (5.6%)
Total Terminations not 'Per Study'	102 (10.0%)	91 (8.8%)

a. Data from NDA vol. 2.315, table 8.1B.

Non-Bleeding Adverse Events

The incidence of AEs not related to bleeding were infrequently reported, and was similar in the two treatment groups. See ESPRIT study report, appendix table 14.3.51 for details.

Rehospitalizations

Rehospitalizations occurred at similar rates in both groups during the first 30 days after therapy.

Table 3.4.2.9 Rehospitalizations within 30 Days in ESPRIT[a].

Rehospitalizations	Placebo (N = 1024)	Eptifibatide (N = 1040)
Total Hospitalizations Within 30 days of Randomization	69 (6.7%)	73 (7.0%)
Cardiovascular Reason	44 (4.3%)	45 (4.3%)
Non-cardiovascular Reason	22 (2.2%)	27 (2.6%)
Unknown/missing Reason	3 (0.3%)	1 (0.1%)
Data Not Available	1	1

a. Data from ESPRIT study report, table 12-25.

3.5 Comparison of ESPRIT and IMPACT-II

In addition to the usual issues of efficacy and safety, the use of a novel dosing regimen (along with an altered heparin dosing) in ESPRIT requires a comparison of the event rates seen in ESPRIT with those reported in earlier trials of eptifibatide. In particular, the results of the IMPACT-II trial, which studied the effects of eptifibatide in patients undergoing PCI (with or without stent placement), will be compared with ESPRIT for efficacy and safety. A comparison of the bleeding from all reported trials of GPIIb/IIIa inhibitors can be found in Appendix Four.

Efficacy Comparison between IMPACT-II and ESPRIT

IMPACT-II was a randomized, placebo-controlled trial of eptifibatide in patients undergoing PCI. Patients were randomized to receive one of two doses of eptifibatide, both of which were lower than the ESPRIT trial dose, as shown in the table below. The dose of heparin used was also different, with a lower degree of anti-coagulation targeted in the ESPRIT trial.

Table 3.5.1 Doses of Eptifibatide and Heparin in IMPACT-II and ESPRIT

Study	Dose of Eptifibatide	Heparin Dose
IMPACT-II	135 μg/kg bolus then 0.5 μg/kg/min infusion 135 μg/kg bolus then 0.75 μg/kg/min	140 μg/kg bolus, then infusion with ACT target of >300 to 500 secs
ESPRIT	180 μg/kg bolus the 2.0 μg/kg/min infusion; second bolus of 180μg/kg 10 minutes after start of infusion	60 μg/kg bolus, then infusion with ACT target of 200 to 300 secs

There were other important demographic differences between the two trials. Most significantly, the percentage of patients with ongoing cardiac ischemia in the trial was higher in the IMPACT-II (41%) than in ESPRIT (roughly 14%). The use of ACE-inhibitors was also more common in the ESPRIT trial, as was the use clopidogrel. The rare use of ticlopidine or clopidogrel in IMPACT-II points out another critical difference in the two trials: the use of stents was rare in the IMPACT-II trial but nearly universal in ESPRIT. Finally, duration of therapy was 12 hours after completion of PCI in IMPACT-II, compared with a mean of 18 hours in ESPRIT). The table below summarizes the incidence of the primary endpoint in IMPACT-II (death, MI, or urgent revascularization at 30 days) as well as selected endpoints for comparison with ESPRIT.

Table 3.5.2 Clinical Outcomes from IMPACT-II[a].

Endpoint	Placebo N=1285	Integrilin Low-dose N=1300	Integrilin High-dose N=1286	% Reduction Relative/ Absolute[c]
Death, MI, Urgent Intervention at 48 hours	131 (10.2%)	99 (7.6%)	102 (7.9%)	22.5%/ 2.3%
Death, MI, Urgent Intervention at 30 days	149 (11.6%)	118 (9.1%)	128 (10.0%)	13.8%/ 1.6%
Death/ MI at 24 hours	90 (7.0%)	71 (5.5%)	67 (5.2%)	25.7%/ 1.8%
Death/ MI at 30 days	110 (8.6%)	89 (6.8%)	95 (7.4%)	14.0%/ 1.2%

a. Data from Medical Review of IMPACT-II, dated 1.26.97.

b. Urgent intervention in this trial included stent implantation for threatened or manifest abrupt closure, repeat or urgent or emergency angioplasty, or urgent or emergency CABG.

c. Refers to placebo compared with high –dose eptifibatide.

For comparison, results from the ESPRIT study for similar endpoints and timepoints are summarized below. The relative percent reduction associated with eptifibatide use is substantially larger than that reported for the IMPACT-II study.

Table 3.5.3 Clinical Outcomes in ESPRIT[a,b].

Endpoints	Placebo N=1024	Eptifibatide N=1040	% Reduction Relative/ Absolute
Death, MI, Urgent Intervention at 48 hours[c]	95 (9.3%)	62 (6.0%)	36%/ 3.3%
Death, MI, Urgent Intervention at 30 days[c]	107 (10.4%)	71 (6.8%)	35%/ 3.6%
Death/ MI at 24 Hours	91 (8.9%)	57 (5.5%)	38%/ 3.4%
Death/MI at 30 Days	104 (10.2%)	66 (6.3%)	38%/ 3.8%

a. Data from ESPRIT study report.

b. All events as adjudicated by the Central Events Classification Committee (CEC).

c. Urgent intervention must be in distribution of original lesion.

Safety Comparison between IMPACT-II and ESPRIT: Bleeding Adverse Events

The pivotal safety concern is bleeding. For the IMPACT-II trial, in patients undergoing PCI, only the overall incidence of major and minor bleeding is available to the reviewer.

Table 3.5.4 Bleeding according to TIMI criteria in the IMPACT-II trial[a].

TIMI Bleeding Status and need for transfusion	Placebo (n=1230)	Eptifibatide 135/0.5 (n=1249)	Eptifibatide 135/0.75 (n=1245)
TIMI Major bleeds	55 (4.5%)	55 (4.4%)	58 (4.7%)
TIMI Minor bleeds	115 (9.3%)	146 (11.7%)	177 (14.2%)

a. Data from published paper and from Advisory Committee Briefing Document (1.28.98). Data excludes 147 subjects with insufficient data for analysis.

For the ESPRIT trial, the bleeding rates were lower.

Table 3.5.5 Bleeding Adverse Events in ESPRIT using TIMI Classification[a].

Bleeding Severity (TIMI Criteria)[b]	Placebo (N = 1024)	Eptifibatide 180/2.0/180 (N =1040)
Major	4 (0.4%)	13 (1.3%)
Minor	18 (2.0%)	29 (3.0%)

a. Data from ESPRIT study report, table 12-3.

b. Definitions can be found in Appendix Two (definitions).

The rates of life-threatening bleeding adverse events for the two trials are summarized below. Too few events occurred for strict comparison. There is no evidence, however, that the new regimen eliminated completely the risk of these events.

Table 3.5.6 Life-Threatening Bleeding in IMPACT-II[a].

IMPACT-II	Placebo (n=1230)	Eptifibatide 135/0.5 (n=1249)	Eptifibatide 135/0.75 (n=1245)
Intracranial	1 (0.1%)	1 (0.1%)	2 (0.2%)
Retroperitoneal	0 (0%)	4 (0.3%)	3 (0.2%)

a. Data from IMPACT-II study review, table 8-27.

Table 3.5.7 Life-Threatening Bleeding in ESPRIT[a].

ESPRIT	Placebo (N = 1024)	Eptifibatide 180/2.0/180 (N =1040)
Intracranial	1 (0.1%)	2 (0.2%)
Retroperitoneal	0 (0%)	3 (0.3%)

a. Data from ESPRIT study report, table 12-6.

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3.6 ESPRIT Efficacy and Safety Summary

The ESPRIT trial compared the clinical effects of a novel dosing regimen of eptifibatide to placebo in patients undergoing percutaneous coronary intervention (PCI) with stent placement. In addition to the usual issues of efficacy and safety, the use of a novel dosing regimen (along with an altered heparin dosing) necessitate a comparison of the event rates seen in ESPRIT with those reported in earlier trials of eptifibatide (see section 3.5 above). What follows is a series of conclusions regarding the efficacy and safety of eptifibatide in the post-PCI setting, followed by a summary comparison with IMPACT-II.

Efficacy

1. The ESPRIT trial was adequately designed, powered and conducted to give reasonable reassurance of the trial results. No significant trial conduct issues were identified; one site had its principal investigator disqualified by its IRB, but excluding these patients did not materially alter the interpretation of the trial. **Section 3.3.3 and Appendix 3**

2. ESPRIT enrolled 1024 patients in the placebo group, and 1040 in the group receiving eptifibatide. The randomization schema resulted in two treatment groups that were well-balanced in terms of their demographics, including baseline characteristics, demographics and cardiovascular history. **Section 3.3.4**

3. The pre-specified, primary endpoint of the ESPRIT trial was the incidence of death, myocardial infarction, urgent target vessel revascularization, and need for 'bail-out' therapy within 48 hours, as adjudicated by a Central Events Classification Committee, based on the randomized population. Eptifibatide use was associated with a reduction in the incidence of the primary endpoint from 10.5% (108 events) to 6.6% (69 events). This difference was significant (p=0.0015), and extended to the individual parts of the endpoint with the exception of deaths, where too few occurred for meaningful comparison (3 total through 48 hours). **Section 3.3.7**

4. Approximately 90% of the clinical events through 48 hours were MIs, largely detected through the protocol-specified measurement of CPK levels through the first 24 hours after PCI. These samples were analyzed centrally, and not available to the investigators. As a result, the investigators identified fewer MIs than the CEC (88 fewer at 48 hours), and there was no significant difference between the two treatment groups for the primary endpoint or for the incidence of death/MI when they were analyzed according to the endpoints identified by the investigators. **Section 3.3.8**

5. For the endpoint of death or MI, eptifibatide reduced its incidence at 48 hours by 40% and at 30 days by 39%. **Table 3.3.8.2**

6. The significant reduction in the incidence of the primary endpoint in the eptifibatide group persisted through 30 days, where a 36% reduction in the incidence of the primary endpoint was seen in the eptifibatide group relative (78 events, 7.5%) relative to placebo (120 events, 11.7%), p=0.0011. **Table 3.3.8.1**

7. The effects of eptifibatide on the primary endpoint were also consistent across a variety of sub-group analyses, including age, gender, type of stent used, and medical history at entry. Relatively few non-white patients were enrolled, limiting the trial's power to assess the effect of eptifibatide in this population. **Section 3.3.10**

8. The incidence of bail-out to open-label therapy was measured separately from the primary endpoint. While very few patients received 'bail-out' therapy, bail-out for presumed thrombotic reasons (*e.g.*, suspected stent occlusion) was more common in the placebo group (22 events, 2.1%) than in the eptifibatide group (10, 1.0%). **Table 3.3.8.4**

Safety

9. There were 10 deaths through 30 days in the ESPRIT trial: 6 in placebo and 4 in eptifibatide.

10. More Serious Adverse Events (SAEs) occurred in the eptifibatide group (100 events, 9.6% of enrolled patients) compared with placebo (71, 6.9%). There were also more discontinuations due to AEs in eptifibatide (60, 5.8%) compared with placebo (71, 6.9%). These differences are accounted for by the increased number of serious bleeding events in the eptifibatide group. **Section 3.4.2, Table 3.4.2.8**

11. Bleeding adverse events were classified according to the TIMI and GUSTO classifications. By either measurement tool, eptifibatide use was associated with an increased incidence of bleeding events. In general, these were of mild-to-moderate severity, although the incidence of serious and life-threatening bleeding events (*e.g.*, intracranial hemorrhage, retroperitoneal hemorrhage) was also more common with eptifibatide. The need for transfusion of RBCs was similar in the two treatment groups. **Section 3.4.2, Tables 3.4.2.3 to 3.4.2.6**

Safety (cont)

12. No drug or procedure that also affects hemostasis (*e.g.*, clopidogrel, compression method for femoral access) interacted with eptifibatide to greatly increase the risk of bleeding above that of the eptifibatide group as a whole.

13. Thrombocytopenia was more common in the eptifibatide group (9 events, 0.9%) than in the placebo group (4, 0.4%). **Table 3.4.2.7**

14. Adverse events un-related to bleeding were infrequent and no more common with eptifibatide.

15. The rates of all-cause rehospitalization within the first 30 days, as well as the rate of rehospitalizations for cardiovascular causes, was similar in the two treatment groups. **Table 3.4.2.9**

Comparison with IMPACT-II

16. Important differences between the two trials exist that limit comparison of their safety and efficacy data. **Section 3.5**

17. The rates of clinical events through 30 days in the placebo groups for the two trials are similar. In ESPRIT, the use of eptifibatide was associated with a larger decrease in the event rates for death, MI, and urgent interventions at 24-48 hours and at 30 days. **Table 3.5.2.3, Appendix Four**

18. The rate of bleeding adverse events reported as Major or Minor according to the TIMI classification were lower in the ESPRIT trial than in the IMPACT-II trial. **Tables 3.5.2 and 3.5.3**

19. The rates for life-threatening bleeding events were low in both trials. **Table 3.5.6**

3.7 ESPRIT Medical Reviewer's Conclusions

The efficacy results from the ESPRIT trial are robust and internally-consistent: eptifibatide administered using the new dosing scheme along with ASA, heparin and a thienopyridine (largely clopidogrel) is associated with a significant reduction in the rate of clinically-relevant events (death, MI, urgent revascularization, need for 'bail-out' therapy with GPIIb/ IIIa inhibitor) in patients undergoing PCI with coronary stent placement through 30 days after the procedure. Approximately 90% of the events at 48 hours were MIs, largely detected through the protocol-specified measurement of CPK levels through the first 24 hours after PCI. These samples were analyzed centrally, and not available to the investigators. As a result, the investigators identified fewer MIs than the CEC (88 fewer at 48 hours), and there was no significant difference between the two treatment groups for the primary endpoint or for the incidence of death/MI when they were analyzed according to the endpoints identified by the investigators. The effect on the incidence of death, MI and need for urgent revascularization extends to all of the relevant clinical sub-groups with sufficient data including women. This latter finding is relevant given the ambiguous findings from the PURSUIT trial as related to the effects of eptifibatide in women with Acute Coronary Syndrome. There were too few non-whites included in the trial to allow a robust analysis, but the point estimate for the primary endpoint, based on the numbers enrolled was consistent with a positive effect of eptifibatide in this group as well. When compared with IMPACT-II, the rate of events in the placebo groups were similar; however, the higher dose of eptifibatide in ESPRIT (along with other important differences in patient demographics and treatment) was associated with a greater decrease in the incidence of death, MI, and need for urgent revascularization.

With regard to safety, the ESPRIT results are important for another reason. First, the trial used a lower target heparin dose than the currently recommendations in the Integrilin label, which is based on the protocol-specified ACT targets used in the PURSUIT and IMPACT-II trials. In the ESPRIT trial, reducing the amount of heparin used also decreased, but did not eliminate the bleeding that accompanies the use of GPIIb/IIIa inhibitors. This reduced bleeding was seen in both the Major and Minor TIMI bleeding, although too few events occurred to determine whether there was a decrease in the incidence of serious and life-threatening bleeding (*e.g.*, retroperitoneal, intracranial). There is, however, no evidence that the lowered dose of heparin has eliminated the risk of life-threatening bleeding associated with GP IIb/IIIa use. Of interest, this reduction in the incidence of bleeding has occurred despite the use of a higher dose of eptifibatide and the routine use of thienopyridines (clopidogrel, ticlopidine) in ESPRIT. An unknown is the impact of recent developments in the management of hemostasis after PCI. In a series of analyses looking at the interaction of eptifibatide with other drugs and procedures affecting hemostasis, no factor was identified that interacted with eptifibatide to greatly increase the risk of bleeding above that seen in the overall eptifibatide population taking.

The results of the ESPRIT trial should certainly be reflected in the approved label of eptifibatide, including an indication for the use of eptifibatide in patients undergoing PCI with stent placement. The lowered dose of heparin during PCI, including the lowered target ACT, should also be included in the label as an aide to reduce the bleeding complications associated with the use of GP IIb/IIIa inhibitors. Recommendations concerning those labeling changes are to be found in Appendix Five.

4.0 Appendix One: Key Personnel

DSMB Members

1. Christopher Cannon, MD Chairman
   Brigham and Women's Hospital
2. Peter Berger, MD
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5. Dorothy J. Brown
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5.0 Appendix Two: Key Definitions

GUSTO Classification

Mild: Bleeding which does not result in hemodynamic compromise or blood transfusion.

Moderate: Bleeding that requires transfusion of blood, but which does not lead to hemodynamic compromise requiring intervention.

Severe or life threatening: Intracranial hemorrhage, or other bleeding that causes hemodynamic compromise and requires intervention.

TIMI Classification

Minor: Gross hematuria or hematemesis, observed blood loss associated with a drop in hematocrit of >9% or a drop in hemoglobin of >3 gm/dL that does not meet the criteria for a major bleed.

Major: Intracranial hemorrhage; or clinically significant overt hemorrhage (bleeding at an observed site) associated with a drop in hematocrit of >15% or a drop in hemoglobin of >5 gm/dL. When calculating the fall in hemoglobin or hematocrit, a transfusion of one unit of blood prior to determination of bleeding severity will be considered equivalent to a 1 gm/dL fall in hemoglobin and a 3% fall in hematocrit. •

Thrombocytopenia

Thrombocytopenia is a decline in platelet count as follows:: platelet count <100,000/ mm^3 or >50% reduction from baseline.

Profound Thrombocytopenia: platelet count <20,000/mm^3

Hematoma - A localized, indurated mass of extravasated blood >5 cm that is relatively or completely confined within a tissue space. •

Retroperitoneal Hemorrhage - Bleeding into the retroperitoneal space documented by CT scan. •

Gastrointestinal (GI) Hemorrhage - Bleeding from gastrointestinal tract •

Genitourinary (GU) Hemorrhage - Bleeding from the genitourinary tract •

Respiratory Hemorrhage - Bleeding from the respiratory tract

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6.0 Appendix Three: Analyses Excluding

The sponsor notified the FDA on 2.13.01 that one of the principal investigators in the ESPRIT study had been removed from clinical work at his institution 'as a result of problems in a clinical trial not related to ESPRIT.' The table below summarizes the results for the primary endpoint excluding patients . The primary efficacy analysis was the composite of death, MI, urgent target vessel revascularization (UTVR) and the use of 'bail-out' therapy (TBO) at 48 hours.

Primary Endpoint from ESPRIT Excluding

48-Hour Endpoint	Placebo N=1009	Eptifibatide N=1026	% Reduction Relative/Absolute	Relative Risk (95% C.I.) p-Value
Death/MI/UTVR/TBO at 48 Hours[c]	106 (10.5%)	67 (6.5%)	38%	0.60 (0.43, 0.82) 0.0013
Death/MI/UTVR	93 (9.2%)	60 (5.8%)	37%	0.61 (0.44, 0.86) 0.0040

a. Data from COR fax dated 2.27.01.
b. All events as adjudicated by the Central Events Classification Committee (CECC).
c. The pre-specified primary endpoint.

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8.0 Appendix Four: Bleeding Events in Other Trials with GP IIb/IIIa Inhibitors

The tables below summarize the occurrence of TIMI-class major bleeding in the major trials of intravenous GP IIb/IIIa inhibitors with available data. Where available, data on the need for transfusions is also included. The first table below summarizes the patient populations enrolled in each of the trials (ACS vs. post-PCI). The two primary trials in Acute Coronary Syndrome (ACS) were PRISM-PLUS and PURSUIT. The remainder, with the exception of the smaller PRISM trial, were conducted in patients undergoing PCI with or without stent placement.

Trial Populations in Major Trials with GPIIb/IIIa Inhibitors.

Trial	ACS	Post-PCI
Tirofiban (Aggrastat)		
PRISM	X	
PRISM-PLUS	X	
RESTORE		X
Eptifibatide (Integrilin)		
IMPACT-II		X
PURSUIT	X	
ESPRIT		X
Abciximab (Reopro)		
EPIC		X
EPILOGUE		X
CAPTURE		X
EPISTENT		X

A. Aggrastat (Tirofiban)

In the three trials using tirofiban with available data (TARGET has not been submitted to the Agency) there was a higher incidence of TIMI-major and minor bleeding in the tirofiban+heparin group, compared to heparin alone. Protocol-specified major bleeding was also increased in the tirofiban +heparin arm in all three trials, especially the RESTORE trial.

Occurrence of Major Bleeding in Trials with Tirofiban[a].

	Placebo (Heparin)	Tirofiban (no Heparin)	Tirofiban (+Heparin)
PRISM-PLUS			
TIMI Major bleeds	6 (0.8%)	9 (2.6%)	11 (1.4%)
TIMI Minor bleeds	64 (3.8%)	35 (10.1%)	81 (10.5%)
PRISM			
TIMI Major bleeds	6 (0.4%)	7 (0.4%)	
TIMI Minor bleeds	31 (1.9%)	33 (2.0%)	
RESTORE			
TIMI Major bleeds	17 (1.6%)		24 (2.2%)
TIMI Minor bleeds	67 (6.3%)		129 (12.0%)

a. Data from individual trial reports.

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B. Reopro (abciximab)

The first table below shows the incidence of major and minor bleeding from the three efficacy trials performed as part of the Reopro NDA.

Incidence of bleeding within 30 days in Trials with Reopro (Abciximab)[a].

	Placebo	Abciximab +High-dose Heparin[a]	Abciximab +Low-dose Heparin[a]
EPIC Trial[c]	n=696	n=708	
TIMI Major bleeds	46 (7.0%)	99 (14.0%)	
TIMI Minor bleeds	N/A	N/A	
Requiring Transfusion	49 (7.0%)	109 (15%)	
CAPTURE Trial	n=635	n=630	
TIMI Major bleeds	12 (1.9%)	24 (3.8%)	
TIMI Minor bleeds	13 (2.0%)	30 (4.8%)	
Requiring Transfusion	21 (3.4%)	44 (7.1%)	
EPILOG Trial	n=939	n=918	n=935
TIMI Major bleeds	29 (3.1%)	32 (3.5%)	19 (2.0%)
TIMI Minor bleeds	35 (3.7%)	37 (4.0%)	68 (7.4%)
Requiring Transfusion (PRBCs)	37 (3.9%)	30 (3.3%)	18 (1.9%)
EPISTENT Trial	N=809		N=794
TIMI Major bleeds	18 (2.2%)		12 (1.5%)
TIMI Minor bleeds	14 (1.7%)		23 (2.9%)
Requiring Transfusion (PRBCs)	23 (2.8%)		17 (2.2%)

a. High and low refers to the heparin bolus and the ACT target in the respective trials (200-250 or 300-350 respectively).

C. Integrilin (eptifibatide)

Summaries of the bleeding events according to severity (TIMI criteria) for the PURSUIT, IMPACT-II, and ESPRIT trials are shown below. The trials are shown separately because of the different dosing of eptifibatide used.

Bleeding within 30 days according to TIMI criteria in PURSUIT[a].

	Placebo (n=4696)	Eptifibatide 180/2.0 (n=4679)
TIMI Major bleeds	425 (9.3%)	498 (10.8%)
TIMI Minor bleeds	347 (7.6%)	604 (13.1%)
Requiring transfusion	438 (9.3%)	550 (11.8%)

a. Data from NDA 20-718 and primary medical officer review (Dr. Isaac Hammond).
b. Transfusion with either packed RBCs or whole blood.

For the IMPACT-II trial, in patients undergoing PCI, only the overall incidence of major and minor bleeding is available to the reviewer.

Bleeding according to TIMI criteria in the IMPACT-II trial[a].

TIMI Bleeding Status and need for transfusion	Placebo (n=1230)	Eptifibatide 135/0.5 (n=1249)	Eptifibatide 135/0.75 (n=1245)
TIMI Major bleeds	55 (4.5%)	55 (4.4%)	58 (4.7%)
TIMI Minor bleeds	115 (9.3%)	146 (11.7%)	177 (14.2%)

a. Data from published paper and from Advisory Committee Briefing Document (1.28.98). Data excludes 147 subjects with insufficient data for analysis.

C. Integrilin (eptifibatide) (cont)

The table below summarizes the bleeding adverse events categorized per the TIMI classification from ESPRIT.

Bleeding Adverse Events in ESPRIT using TIMI Classification[a].

Bleeding Severity (TIMI Criteria)[b]	Placebo (N = 1024)	Eptifibatide 180/2.0/180 (N =1040)
Major	4 (0.4%)	13 (1.3%)
Minor	18 (2.0%)	29 (3.0%)

a. Data from ESPRIT study report, table 12-3.
b. Definitions can be found in Appendix Two (definitions).

D. Life-Threatening Bleeding

The last table summarizes the limited number of life-threatening bleeding events that were reported in the databases of the GP IIb/IIIa inhibitors tirofiban and eptifibatide.

Occurrence of Life-Threatening Bleeding AEs with Tirofiban[a].

	Tirofiban (N=2032)	Tirofiban+ Heparin (N=1953)	Heparin (N=3546)
PRISM-PLUS			
Retroperitoneal bleeds	2	0	1
Intracranial bleeds	0	0	0
Cardiac tamponade	1	2[b]	0
PRISM			
Retroperitoneal bleeds	1	0	1
Intracranial bleeds	2	0	2
Cardiac tamponade	1	0	1
RESTORE			
Retroperitoneal bleeds	0	6	3
Intracranial bleeds	0	1	3
Cardiac tamponade	0	2[d]	1
Overall			
Retroperitoneal bleeds	3 (0.15%)	7 (0.46%)[c]	5 (0.14%)
Intracranial bleeds	2 (0.098%)	1 (0.05%)	5 (0.14%)
Cardiac tamponade	1 (0.05%)	4 (0.20%)	2 (0.06%)

a. Data from individual trial reports and validated with the sponsor.
b. Both IC bleeds occurred at day 11 and day 14 (post-study drug).
c. One retroperitoneal bleed took place in protocol 007 (AN 241), occurring on day 1 of study drug administration.

The rates of life-threatening bleeding AEs for the IMPACT-II and ESPRIT are summarized below.

Life-Threatening Bleeding in IMPACT-II[a].

IMPACT-II	Placebo (n=1230)	Eptifibatide 135/0.5 (n=1249)	Eptifibatide 135/0.75 (n=1245)
Intracranial	1 (0.1%)	1 (0.1%)	2 (0.2%)
Retroperitoneal	0 (0%)	4 (0.3%)	3 (0.2%)

a. Data from IMPACT-II study review, table 8-27.

Life-Threatening Bleeding in ESPRIT[a].

ESPRIT	Placebo (N = 1024)	Eptifibatide 180/2.0/180 (N =1040)
Intracranial	1 (0.1%)	2 (0.2%)
Retroperitoneal	0 (0%)	3 (0.3%)

a. Data from ESPRIT study report, table 12-6.

Overall, too few events occurred for meaningful comparison between the products or regimens. There is no evidence that the lowered dose of heparin (as used in ESPRIT) eliminated the risk of life-threatening bleeding associated with GP IIb/IIIa use.

9.0 Appendix Five: Proposed Label (With Revisions)

Below are my comments on the changes proposed to the approved label by the sponsor. Changes suggested by the sponsor appear as underlines in black. Places where they have suggested striking language from the current label appear as black strike-throughs. My recommended additions/deletions appear in color.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

52 pages redacted from this section of the approval package consisted of draft labeling

(pp. 33 - 84)

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
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Rockville, MD 20816
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Memorandum

DATE: 4.26.01

FROM: Douglas C. Throckmorton, M.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Raymond Lipicky, M.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: 120-Day Safety Update from the ESPRIT Trial.

PURPOSE OF MEMO

This memorandum reviews the 120-day Safety Update, submitted by COR Therapeutics on 2.7.01 as part of the Inegrilin Annual Report.

MATERIALS USED FOR REVIEW

1. IND [redacted] serial 312.

DATA REVIEW AND CONCLUSIONS

I reviewed the safety update from the ESPRIT study contained in the Annual Report. These data do not affect my conclusions regarding the safety of Integrilin when used as described in the ESPRIT trial. These conclusions can be found in my original review of the ESPRIT supplement.