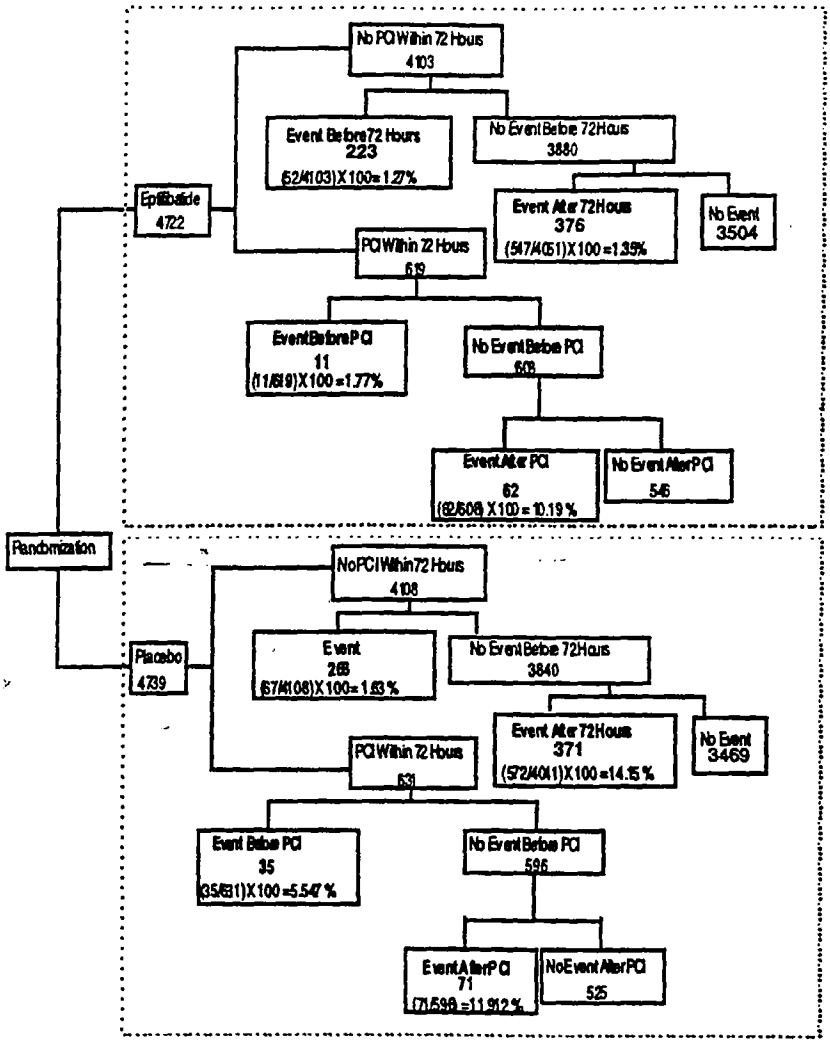

The following table summarizes this arbitrary, post-hoc look at the results of PURSUIT. The **"Study as a Whole"** is the study result that is the 30-day, intent-to-treat analysis that had a p of 0.042. That result is displayed as the number of events observed in the placebo group [745], the number of events observed in the eptifibatide group [672], the difference in observed events [745 - 672] and that difference expressed as an event rate prevented by treating 100,000 patients [1,550/100,000] (using the number of patients treated with eptifibatide group [4722] as the number of patients at risk).

	Placebo	eptifibatide		
Study as a Whole	745	672	73	1,550/100,000
		Non-PCI Patients		
Events after 72 hours	371	376	-5	0/100,000
Events before 72 hours	268	223	45	1,096/100,000
Overall Non-PCI Population	639	599	40	975/100,000
		PCI Patients		
Events after 72 hours	71	62	9	1,480/100,000
Events before 72 hours	35	11	24	3,878/100,000
Overall PCI Population	106	73	33	5,331/100,000

It seems apparent that the treatment effect in patients that receive PCI within 72 hours (not the eptifibatide treatment outcome of PCI, but the treatment effect that is present in the group of patients that received PCI because of their clinical state at the time) is from 1000s of times (events after 72 hours) to 5 times (overall populations) greater than in the group t did not receive PCI within 72 hours. I recognize that this analysis is not based upon a randomized population and that the treatment effect may be a confounder, but when signals approach orders of magnitude (and there are plenty of events in the non-PCI patients after 72 hours), it is hard to think such a signal has no meaning.

The sponsor says that "The fact that patients undergoing revascularization within 72 hours appear to experience the greatest treatment benefit may be explained by a selection bias, which directed patients with the most clear-cut disease (and thus most likely to benefit from antiplatelet therapy) to a therapeutic intervention. However, these patients cannot be identified a priori, hence the need to treat all patients. This is sound strategy, since the remaining patients exhibited little increase in bleeding risk and still appeared to benefit from eptifibatide therapy."

The "may be explained by a selection bias" is certainly acknowledged and may be correct, and not being able to a priori identify patients who are most likely to benefit is certainly correct. But I have a single trial to base conclusions upon and I am looking for a reasonably clear identification of the patient population that benefitted (other than identify them simply by the process of randomization). The clearest thing I see, is that the patient population that certainly benefitted was only 13% of the population randomized to eptifibatide (the PCI treated patient population, n = 619 in the eptifibatide group) and see that another 82% of the population randomized to eptifibatide (Non-PCI patients that did not have an event within 72 hours, n = 3880 in the eptifibatide group) has a subgroup point estimate in the wrong direction; more events in the eptifibatide treated population. That does not give me great deal of comfort. To me it makes the statement "hence the need to treat all patients" non-dispositive; neither ruled in or out. (Note there is another 5% of the randomized population to account for, and I will).

As I see it, I am willing to acknowledge a favorable treatment effect of eptifibatide in patients undergoing PTCA (based on the **IMPACT II** trial, in the low dose group **2,385 events prevented/100,000** patients and in the high dose group **1,633 events prevented/100,000** patients treated), so my interest focuses upon the events that occurred prior to PCI. If this were a substantial effect, I could possibly accept the argument that it was important to start eptifibatide as soon as possible, not simply after one had already decided that PTCA needed to be performed.

Still looking for the signal that would convince me that "hence the need to treat all patients" is correct, I focus upon the **events that occurred prior to PCI** in the patients that received PCI prior to 24 hours. There were 24 such events. Were one to treat all patients simply to get this effect (and expect this effect to be in addition to the beneficial effect upon PTCA which would have occurred if one waited until that decision was made), the events prevented would be 24/9461 randomized patients or **243 events prevented/100,000** treated patients. Pretty small, I would say and pretty unreliable even though I got a Chi square $p < 0.001$; not very robust because of the small number of events. So, this does not convince me that "hence the need to treat all patients" is an obviously correct interpretation of the findings.

So I am left with the 5% of patient randomized to eptifibatide, those 223 patients that had an event prior to 72 hours. Looks real enough, accounts for 55% of the events recorded in the whole trial. The number of events prevented is 40 out of a total of 1238. I guess it is real. Since the trial as a whole barely achieved statistical significance, I can hardly claim that this finding has even 1 chance out of 20 of being "true". So, I

can only say that I am still unconvinced. Could be true that "hence the need to treat all patients" is a correct inference, but I cannot say that it is proved by this single trial and I have only this single trial to draw my inference from.

Of some importance, if one is looking for empirical confirmation of IMPACT II results, is the treatment effect seen in those patients that had PCI within the first 72 hours of randomization. There were 78 events in the placebo group and 64 events in the eptifibatide group. My estimate of the

"PCI Treatment Effect" = (71-62) = 9 events prevented,
there were 608 patients in the eptifibatide group so 14/608 = 2.30 %,
says that **2,300 events** would be **prevented/100,000** treated patients.

A point estimate about that for the trial as a whole and about that of IMPACT II. Numbers, however, are pretty small. The outcome of all patients that had PCI by 72 hours certainly gives me confidence with the inference that such patients would benefit from eptifibatide is correct.

I end up thinking that PURSUIT, as a stand alone trial, does not support early intervention and would therefore not be dispositive for a claim in "unstable angina." The results are consistent with waiting until one has decided that PCI is "almost certain" (about 13 % of the population entered). The results of PURSUIT confirm the results of IMPACT II (or visa versa).

Adverse Effects

Outside of hemostasis (and perhaps, anaphylaxis and other side effects; see below), there do not appear to be any systemic effects nor organ system involvements that can be detected in the randomized trials. With the exception of bleeding, hypotension and shock (seemingly related to the bleeding status), and thrombocytopenia, from analyses that have been conducted, it is not possible to distinguish serious adverse effects in the eptifibatide group from those of the placebo group.

The complexity of the clinical setting is clear from the numbers of patients that did not complete a full 72 hours of infusion of either placebo (1,466 patients, 31.3% of those randomized) or the high dose eptifibatide (1,477, 31.1% of those randomized), this difference having a p = 0.001. The sponsor states that most discontinuations were because patients were discharged prior to the 72 hour time of infusion, by physician preference. On the other hand, of the discontinuations due to bleeding, 11% were in the eptifibatide group and 1% in the placebo group (an order of magnitude difference). (COR says the numbers are 8% and 1% Table 8-39, PURSUIT Final Report, Vol 2.47, page 268). This difference in estimates is not resolved, but need not be resolved; they say the same thing.

Animal Data.
In rats and rabbits the biggest non-lethal dose of eptifibatide studied was 500 micrograms/kg/min given for 90 minutes. No larger doses were studied. The greatest human dose infused has been 2.0 micrograms/kg/minute. Thus there appears to be little systemic toxicity to expect. This was confirmed in 3 day, 14 day, and 28 day continuous infusions in rats and monkey at doses up to 72 micrograms/kg/min in rats and 18 micrograms/kg/min in monkeys, where the only detectable effects were related to bleeding.

Other names for eptifibatide that might be encountered are intrifiban, C-68-22 and SCH 60936 injection.

There were no drug effects that affected reproduction in standard Segment I and Segment II pregnancy tests in rats. Three groups of 3 guinea pigs each were tested for eptifibatide antigenicity with no findings and no positive control, and 3 groups of 10 female mice were tested for delayed-type hypersensitivity with similar no findings and no positive control. In standard mutagenicity assays, no mutagenic potential was found. There were no chronic toxicology studies longer than 28 days duration.

Of interest is that in rabbits, over a dose range of 10, 50, and 100 micrograms/kg/min infusion, there were dose related declines in platelet counts were observed. Seems that this effect is unique to rabbits (and? man).

Anaphylaxis and "other side effects."
I bring this up to counter a draft of this memorandum that you may have seen. Dr. Hammond in his review (Appendix 6, reasons for discontinuation due to Adverse Events other than Bleeding) has 3 cases of anaphylaxis listed, all in the eptifibatide group. That is correct. However, there were a total of 17 anaphylaxis events, but only 3 discontinuations due to anaphylaxis. Of the 17 cases, 7 were in the placebo group, 7 were in the eptifibatide 180/2.0 group and 3 were in the eptifibatide 180/1.3 group. So, indeed, this seems to be no problem, and is consistent with the 9 guinea pigs studied.

Stroke. Stroke was well documented and was evaluated by both the CEC and investigators. As was the case for myocardial infarction, the numbers differ, depending upon the evaluator (CEC or investigator), but in the case of stroke were not very different.

	CEC		Investigator	
	Placebo n=4,739	eptifibatide n=4,722	placebo n=4,739	eptifibatide n=4,722
Total Stroke	39	32	44	33
Hemorrhagic	2	3	5	4
Infarction	33	27	31	27
Infarction with hemorrhage	2	0	not classified	not classified
Type uncertain	3	0	7	2
Missing	0	0	2	0

Stroke, over 30 days, does not seem to have been affected by eptifibatide treatment.

Thrombocytopenia. Dr. Hammond in his review, page 33, states that in the SAS data set labelled "AE" there were 3 cases of thrombocytopenia in the placebo group and 11 in the eptifibatide group. In another SAS data set labelled "drugadm" there were 15 for placebo and 30 for eptifibatide.

The sponsor, states that in the NDA study report there were 2 in the placebo group and 9 in eptifibatide group. One case in the placebo group was an error and 2 cases in the eptifibatide group were also an error. This makes the "real circumstance" to be 1 case in the placebo group, and 5 cases in the eptifibatide group (which the sponsor does not thinks to be meaningful). The sponsor also points out that this ambiguity of numbers revolved around identifying cases by platelet counts less than 20,000/ microliter. If they define thrombocytopenia at less than 100,000/microliter, there was no difference between groups (but then they do not think that 5 to 1 is a difference either). I am left with the thought that thrombocytopenia can be induced by integrilin but it is uncommon.

More importantly, at the present time I do not know how to resolve the differences between what is found in the SAS data sets, and what the sponsor says. We will, however, ask the sponsor (who will in turn have to ask Schering Plough, since it was Schering Plough that prepared the SAS data sets for submission).

Hypotension and shock. It is clear enough (Table R.24, page 26, of Dr. Hammond's review) that the incidence of hypotension and shock are related to the severity of bleeding (TIMI bleeding status); nearly a quarter of patients with TIMI major bleeds having hypotension or shock. I think the table is also consistent with the statement that for any category of TIMI bleeding (except insignificant or none), the incidence of hypotension and shock is greater in the eptifibatide group than in the placebo group.

What is not clear is whether hypotension and shock are due to something other than hemorrhage in the eptifibatide group or that eptifibatide bleeding is more severe than the TIMI grade gives it credit for. Although this observation is numerically correct, the sponsor points out that it cannot have much meaning since the incidence of death and/or myocardial infarction in those patients that had a TIMI major bleed was 28.8% in the eptifibatide group and 33.2% in the placebo group. So, I guess that observation means nothing, or at least I cannot make sense out of it.

Bleeding. This is complicated to dissect. All patients were receiving aspirin and heparin in addition to eptifibatide and the association/dissociation of eptifibatide to observed bleeding is difficult. The tables found in Dr. Hammond's review nicely describe the observations related to bleeding in PURSUIT. All numbers (reviews, sponsor's briefing document, sponsor's slides) tracking intent-to-treat and "treated-as-randomized," TIMI grade, GUSTO grade, etc. and finally IMPACT II and PURSUIT make precision difficult to document. But, I don't think precision is needed.

Anywhere one looks, bleeding is a problem in both the placebo groups (e.g., incidence of TIMI major bleeding = 9.3%) as well as in the eptifibatide groups (e.g., incidence of TIMI major bleeding = 10.8%), with overall rates of any bleeding approaching 25% of patients randomized. Transfusions were required in 2.4% (2,400 per 100,000 patients treated, approaching the "treatment effect" described above). More patients in the high dose PURSUIT eptifibatide group required transfusions than did those in the placebo group (with about half of those transfusions being between 3 to 10 units of blood). Although stated above and therefore repetitive, discontinuations due to bleeding were 11% in the eptifibatide group and 1% in the placebo group. So, it is clear that the addition of eptifibatide to heparin and aspirin cause more bleeding, but bleeding is part of standard therapy and in the absence of eptifibatide.

Bleeding that causes hypotension and/or shock could be bad for patients with myocardial ischemia. The sponsor points out that it were, and the bleeding associated with the addition of eptifibatide worse than in its absence, the treatment effect of eptifibatide would not have been detected. Yet, there is a "net benefit," so eptifibatide bleeding does not have an observable down side. Nothing wrong with that logic.

Overall bleeding problems were mainly associated with CABG accounting for 62% of the eptifibatide total major bleeding and the placebo major bleeds (CABG accounting for 75% of the total bleeds in that group) and eptifibatide group could not be statistically distinguished from the placebo group either with respect to incidence or severity of bleeding.

Bleeding from the femoral artery access site for either angiography or percutaneous coronary intervention (together accounting for 23% of major bleeds) was the next most common procedure associated with bleeding phenomena. In this circumstance the eptifibatide group experienced problems with about twice the frequency of the placebo group.

Other bleeding was retroperitoneal, oropharyngeal, genitourinary, lower gastrointestinal, upper gastrointestinal, and pulmonary bleeding. Each with an incidence from twice to 10 times as common in the eptifibatide group than in the placebo group. So there is no question that adding eptifibatide to heparin and aspirin causes bleeding as a consequence of the addition of eptifibatide. That is no surprise and sort of "to be expected." There is no way even to get an inkling with respect to what the contribution of heparin and aspirin might be to the phenomenon. For sure, eptifibatide increases rates only a little (50% for TIMI major bleeds and 75% for TIMI minor bleeds), on top of heparin and aspirin. It would be nice to know one really needed one or the other or both, since one or the other or both increases bleeding compared to "none" (referring to persons walking around, not receiving heparin or aspirin) by orders of magnitude, but one doesn't know.

The perspective is that (compared to heparin and aspirin, which are accepted as standard therapy) the bleeding rates associated with use of eptifibatide are "acceptable." The Advisory Committee at the January 28, 1998 meeting was asked that question twice (once for IMPACT II and then again for PURSUIT). Both times they said "yes, acceptable." That doesn't mean they were comfortable, and in fact, for PURSUIT, were clearly uncomfortable, but on its face the rates of bleeding produced by eptifibatide were not "unacceptable."

The rate of TIMI major bleeding seen on the high dose of eptifibatide in PURSUIT was 10.8 %, compared to 9.3 % in the placebo group. Major bleeding by this definition is equivalent to about 3 to 5 units of blood (a drop in hematocrit of 15 units). In my thinking, that is indeed major. Minor bleeding on that scale is up to 2 to 3 units. Even that qualifies, for me, as not insignificant. Two units of blood lost acutely definitely affects blood pressure and heart rate. The intimate association between hypotension/shock and the TIMI grade of bleeding observed in the trials further attests not only to the importance of blood volume to blood pressure, but also to the complexity bleeding introduces to an already complex clinical care setting.

An important comparison to make, that is also the weakest because it is across trials, is a comparison of major bleeding observed in IMPACT II and PURSUIT, excluding CABG-related bleeding. This comes from the sponsor's slide shown at the Advisory Committee meeting (ML-121).

	IMPACT II			PURSUIT	
		eptifibatide	eptifibatide		eptifibatide
	placebo	135/0.5	135/0.75	placebo	180/2.0
	1.7%	2.7%	2.7%	1.1%	4.3%

The placebo rates of major bleeds are about the same in the two trials, but that of the eptifibatide group of PURSUIT as about twice that observed in either arm of IMPACT II

Minor Glitches

Again. it is of some importance to note the graph on page 25 of the sponsor's Advisory Committee briefing document. This relates to the "non-square wave" nature of the 180/2.0 bolus infusion regimen used in PURSUIT (or really any regimen). Plotted on Figure 3-2 is the mean platelet aggregation data that was obtained during a bolus infusion regimen. The thing to note is at 1 hour, the mean platelet aggregation inhibition is less than at 5 minutes and then after 1 hour it increases again to stay level for several days.

As pointed out previously, Dr. MaryAnn Gordon has a table that indicates the % of patients with $\geq$ 80% platelet inhibition as a function of time. Around the 1st hour, there is a substantial number of persons that have less than 80% platelet inhibition effect. So the plasma concentrations achieved with this regimen are not square waves and the little overshoot and rebound of the plasma level curves may have some clinical relevance.

Summary

From my view, and I think that I reasonably (but not exactly) reflect the majority of the Advisory Committee thinking, neither IMPACT II nor PURSUIT are convincing enough to gain approval of eptifibatide, when either viewed in isolation and alone. When asked if they thought that either trial was the equivalent of what they would consider a single trial that met their usual threshold for recommending approval, the Advisory Committee responded with "not quite." I agree with that evaluation.

IMPACT II at best showed an effect that had about 1 chance in 10 or 20 of being wrong, when evaluated by its prospective endpoint. This is not very convincing any way you cut the cake. But a good story can be told if one looks at the results retrospectively and puts the data together and emphasizes only some of the observations. So, its not that there is no information in IMPACT II, there is, but it cannot be viewed as dispositive.

PURSUIT is stronger, but in isolation, still with something only on the order of 1 chance in 20 of giving the wrong inference, when evaluated by its prospective endpoint. There is however a wealth of internal consistency as well as duplicating much of the phenomenology that describes the results of IMPACT II (like, a stronger early effect, having the strongest signal in those patients who had a percutaneous coronary intervention, the early effect preserved from 30 days to 6 months, etc.).

The two studies together are very convincing. It is entirely reasonable (less than 1 chance in around 800 to 1000 of being wrong) to infer that eptifibatide decreases the risk of irreversible events in patients who have a disease that everyone thinks have morbid and mortal events that are strongly determined by the phenomenon of platelet aggregation. Everyone agrees (the sponsor, all reviewers, the Advisory Committee, I and many others) that the totality of randomized controlled trial evidence supports approval of eptifibatide.

The problem is simply what patients should receive eptifibatide? Two different combined endpoints were prespecified, so how should the aim of therapy be described? Four different doses were studied and one of the four pretty clearly doubled (compared to the lowest dose studied) the incidence of a very undesirable side effect (the need for transfusions of up to 10 units of blood), without any clear evidence of increasing the benefit, so what dose should be used?

The patient population that benefits and the aim of treatment? This is a priority application because a claim for unstable angina (the claim the sponsor thought was supported by their trials) would be entirely new and another IIB/IIIa (eptifibatide would be the 2nd) antagonist would be introduced to the market place with the intended use being a patient population for which IIB/IIIa antagonists have not yet been indicated (although we know one other drug in the class is effective in the PTCA setting). So, an indication for "unstable angina" would be a new claim and the eptifibatide studies could have been sufficient; we made that priority decision, and I agree with that decision.

PURSUIT, the single trial that randomized a patient population with unstable angina, barely makes conventional statistical criteria and it is entirely reasonable (although not the only view) to view its major strength (from the point of view of the biological signal it detected) as being derived from patients who had percutaneous coronary intervention, not from the majority of patients randomized. Can that signal be confirmed? Well, there is IMPACT II, which in a properly randomized study and the result are consistent with a benefit from use of eptifibatide in this setting. In combination with the results of PURSUIT, IMPACT II offers enough support to cross my threshold for approval for use in the setting of PTCA (one could also argue vice versa, that is PURSUIT confirmed IMPACT II, which is what the Advisory Committee did). I am confident that a patient population sufficiently at risk to warrant percutaneous coronary intervention will derive a treatment benefit, and I think I can identify the treatment benefit that would be derived (namely decreased incidence of mortality, and decreased incidence of myocardial infarctions). Each study contributes its major strength of evidence to that inference. Neither study alone could have crossed my threshold for that patient population for any named treatment benefit. Of course a repeat IMPACT II at a different dose that found a conventional significance treatment benefit of eptifibatide would also have crossed my threshold for approval. So, the use of eptifibatide in patients who "need" percutaneous intervention is clear enough.

Now, how about use in "unstable angina"? One argument that supports approval for "unstable angina" is that PURSUIT randomized all patients with clinically identifiable "unstable angina" and there was a statistically significant (1 chance in 20 of being wrong) net treatment benefit that favored eptifibatide. That is certainly a reasonable argument. One can say with reasonable certainty that if one treats all patients with "unstable angina", there is for sure no net harm done with respect to the entire population and that the entire patient population **will probably** experience net benefit. It is **will probably**, PURSUIT does not sufficiently prove that, at least from the perspective of prespecified primary endpoints. I am reluctant to award a claim on the basis of this "strength of evidence". Something else is needed in order to come to that conclusion.

In the post-hoc analysis section above I have laid out my reasoning for why that "something else" is not contained within the results of PURSUIT. Although I am convinced by both trials that the antiplatelet effects of eptifibatide should be viewed as providing benefit to patients that have a disease where platelet agglutination is a liability, I can only identify patients in whom a percutaneous intervention is to be performed as being empirically shown to have a benefit. For patients defined by other characteristics I have point estimates of a lesser magnitude of treatment benefit (including greater events in the eptifibatide treated patients in 82% if the randomized population; patients in the eptifibatide group that did not receive PCI and did not have an event within 72 hours). Such results can hardly be considered the basis of approval for a new claim.

Additionally, there is the risk to benefit consideration. The data from PURSUIT provide no compelling argument that there is sufficient benefit in the broad population of unstable angina to warrant the hemorrhagic adverse effects of treatment in the entire population even though there is clearly no mortal adverse effect of early treatment and or bleeding; that is, it is not grossly unsafe. I think that, at least in part, this is what the Advisory Committee said. If they did, I concur with their judgement. To gain my approval recommendation for unstable angina, PURSUIT would have needed far stronger findings and been able to make a more compelling argument for treating earlier than when one has already made the decision that intervention is probably necessary.

What dose? This is also a judgement call. The clinical trials do not establish a dose that should be used. Each of the dosing regimens studied contribute to the decision that eptifibatide should be approved. So, empirically any of them could be used. It is, retrospectively too bad that the 180/1.3 arm of PURSUIT was dropped. For sure, it produced a beneficial treatment effect **2,250 events prevented per 100,000 patients treated** ($0.01<p<0.05$). I t seems from Figure 6-1 (page 123) of the sponsor's Advisory Committee briefing book that the risk of major bleeding is eptifibatide-dose-related, being intermediate between the lower doses of IMPACT II and the 180/2.0 dose of PURSUIT. It is important to note that the PURSUIT "low dose" (namely 180 microgram/kg bolus followed by 1.3 micrograms/kg/minute infusion) found a treatment effect at least as large as that of the "high dose" (namely 180 microgram/kg bolus followed by a 2.0 microgram/kg/minute infusion); the trial result was **1,550 events prevented per 100,000** patients treated.

The Advisory Committee recommended using the dose that they thought had empirical verification in IMPACT II, namely , a 135 ug/kg bolus, followed by a 0.50 ug/kg/min infusion for 20 to 24 hours. They based their choice on the reasoning that an unstable angina claim could not be supported, the high dose in PURSUIT caused bleeding side effects that they thought should narrow the indication, and they needed to pick a dose that had empirically been shown to be "better" than placebo. I think that decision was an error. In fact, the efficacy results of the 180 microgram/kg bolus followed by 1.3 micrograms/kg/minute were not considered at the Advisory Committee meeting.

Certainly any of the dosing regimens in PURSUIT, namely, a bolus followed by an infusion of 72 hours, cannot be practically be used for a PTCA indication. Patients are out of the hospital before the infusion could be terminated. Even in the PURSUIT population, patients were discharged before the 72 hour infusion was complete and early discharge is given as a major reason for the 53% and 59% discontinuations for eptifibatide and placebo, respectively. Of some importance is the fact that there is not even an empirical verification of the dosing regimen (infuse for 72 hours) in PURSUIT itself.

In my view, this issue of what dose to recommend is pretty straight forward to resolve. By any measure or framework of reference, the dosing regimens used in IMPACT II, although producing a measurable efficacy effect, were low and produced a minor bleeding rate. The high dose used in PURSUIT produced a measurable efficacy effect, but was associated with a bleeding rate big enough to be a worry.

From an efficacy point of view, any dose between the low-dose of IMPACT II and the high-dose of PURSUIT should be regarded as differentiable from placebo. The PURSUIT low-dose, produced a lower bleeding rate than did the high-dose and an efficacy effect larger than did the high-dose in PURSUIT. So, a bolus of 180 ug/kg followed by an infusion of 1.30 ug/kg/min should be the one recommended (the PURSUIT low-dose).

The duration of infusion need be no longer than 20 to 24 hours, the usual length of hospital stay.

What about the Guidance Document?

The sponsor has made a point of one (i.e., page 8) section of the existing draft Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. This section deals with studies in a closely related diseases and an excerpt says ..."For example, certain anticoagulant therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the post-angioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant are suitably similar, each study supports the other for each claim."

The questions to the Advisory Committee, in its introduction said "...the Agency specifically suggested that the regulatory requirement for 'independent substantiation,' for an anti-platelet agent, could be met by 2 studies, one in a post-angioplasty setting and the other in acute coronary syndrome, because these settings share some pathophysiological basis. Furthermore, the draft proposal says that 2 such studies would support use in both clinical settings."

The sponsor, at the advice of the Agency in meetings, clearly undertook such a program. Their expectation was that on the basis of a "positive" trial in the post-angioplasty setting and a "positive" trial in unstable angina combined with the Agency recommendations and written Agency guidance, also combined with a strong pathophysiological rationale would result in an Indication for both patient populations.

The development strategy worked eminently well. Eptifibatide is recommended to you for approval. It was turned down once on the basis of IMPACT II alone, and (although not put to the test) I think it would have been turned down on the basis of PURSUIT alone. The results of two trials, together, unequivocally establish a treatment effect of eptifibatide. All patients in the 2 trials had the same disease, namely coronary artery disease. The operational means of identifying patients eligible for treatment were different between the two trials. The results of the trials, however, make it necessary to choose the patient population that should receive treatment. A judgement call that I think excludes treating a population with unstable angina (as did the Advisory Committee).

That is a result dependent conclusion and has no bearing upon the wisdom of the guidance or its general applicability. For example, one parallel dose-ranging trial and one factorial trial would be sufficient to get two antihypertensive products approved, provided both trials showed an antihypertensive effect and the risk/benefit was not unfavorable. The results of the trials are the driving force, not the structure of the general policy.

Other Considerations

I am pleased by the fact that persons who attended the Advisory Committee meeting, outside of Agency personnel as well as members of the Advisory Committee, have taken the trouble to write thoughtful letters regarding the logic of the decision that was made at the Advisory Committee meeting. Although I hope that the practice will not increase (and I do not intend to respond directly to any of them, even though I know that is contrary to your practice), I take it as in the spirit of open communication; I welcome such and do try to champion that attitude.

Just a few of thoughts. Indeed, if you absolutely know from some other frame of reference that IIb/IIIa antagonists are effective, the results of IMPACT II and PURSUIT fall in place, make everything work out well and argue for approval of both indications. All we have, however, are the results of IMPACT II and PURSUIT to consider, as well as knowledge that one other IIB/IIIa antagonist works as an adjunct to PTCA and we have not approached individual drug approval from an acknowledged Baysien view. Maybe we should, but as yet we have not acknowledged that we do.

It is certainly possible, and not unreasonable, to take the position that the "real life" PURSUIT trial, coupled with IMPACT II clearly shows a treatment effect favoring eptifibatide and the end points are morbid/mortal. I do not disagree with that. Then it is not unreasonable to take the position that one should only act upon those things that have been documented by a randomized trial (and not make decisions on the basis of subgroup analyses). I do not disagree with that either. I would still maintain that I do not know who should get treated, but how can that be since I do know who got randomized? That is the problem I tried to lay out above.

Worse yet, I know of development programs where there is more than one trial in "unstable angina" and both trials find statistically significant favorable treatment effects in both trials (based upon the prespecified end-points), but for sure have even less ability to distinguish who benefits and who is harmed. Because, in this case, there are 2 "positive trials," I think the probabilities are that those drugs will be approved for "unstable angina." The results of IMPACT II and PURSUIT are far more distinctive, provide far more information and on the basis of prospective "equity" one could argue that eptifibatide should be approved for "unstable angina." Although such consideration should not be dispositive, and the future is never known with sufficient certainty, it plays a role in my enthusiasm for developing any further arguments.

The facts are pretty well laid out, through the appended written material and the discussion at the Advisory Committee meeting. It is clear that a judgement call is required. At the Advisory Committee meeting, after the facts were laid out (not quite as well as now), I asked the Committee to make a judgement call, to make a decision from a doctor's point of view, as opposed to from a statisticians point of view. They did that. I have also done that in how I structured this memorandum. We are all familiar with the "facts."

Regulatory Problems

Degradation Products Occurring Upon Room Temperature Storage.
The original application provided purity specifications for shelf life (less than 2% degradation products over 24 months of storage at 2 to 8 degrees Centigrade) that were derived from refrigerated storage of

manufactured product. By the test results of 5 or 6 separate lots, degradation products were well under 2%, and the actual shelf life under conditions of refrigerated storage could have been up to 36 months; only 24 months was requested by the sponsor.

Since that time, non-refrigerated storage of the product seems more desirable to the sponsor. The sponsor conducted PURSUIT using mainly non-refrigerated stored product (total exposure being about 9,000 patients with the duration of non-refrigerated storage being from 2 days to 21 months and temperature varying from 2 to 25 degrees Centigrade). Under non-refrigerated conditions, the degradation products get to 10% when stored at 35 degrees Centigrade for 18 months.

There are 8 degradation products (and 7 other impurity chemicals) identified. The sponsor has conducted 6 animal toxicology studies using 4 lots of eptifibatide that were degraded at 45 degrees centigrade; each containing up to 16.5% total degradants. The toxicology studies included cynomolgus monkeys, rats, and rabbits, involved dosing from 14 to 35 days duration, and included Segment I and Segment II reproductive studies . The calculated doses of individual degradants varying from 2 to 51 times the calculated human exposure. The degradation products never being evaluated as single entities but always as the eptifibatide formulation.

There were no findings that differentiated the degraded eptifibatide batches from the toxicology exhibited by non-degraded eptifibatide used in the previous pharm/tox work.

I have no ready interpretation of the studies, although I know that the studies cannot have characterized the effects of the degradants, since in many of the reported studies the concentration of some degradants was below measurement thresholds and that suitable in-vitro mutagenicity and clastogenicity studies have not been performed using the individual degradants. Dr. Resnick in his review of this matter, similarly did not think the animal to be sufficient.

We cannot dissect this problem within the constraints of getting a decision made in time to meet the User Fee deadline. I am reluctant to approve room temperature storage. So, if eptifibatide is approved, I suggest that the shipping and storing be refrigerated, until we can get more information together and/or understand the problem better.

I understand that the sponsor is currently preparing an amendment that will specify that they will ship and store eptifibatide at 2 to 8 degrees centigrade, until this is resolved.

Inspections.
We elected to inspect 3 clinical sites that were involved in the PURSUIT study. One was in Hungary, one was in the Czech Republic and one was in Detroit, Michigan. The results were (all related to the PURSUIT study):

Hungary: 9 items are listed which include: 1) the regional coordinator who signed the form 1572 did not actively supervise nor participate in the conduct of the study, 2) sometimes, the site's sub-investigator did the case-report signing, 3) the physicians who performed study critical functions were not listed on the form 1572, 4) 2 subjects said to have had a myocardial infarction did not and 4 subjects could not be documented as to the duration of ischemic pain required by the protocol, 5) one subject had informed consent signed after the infusion of study drug, 6) 8 subjects had case report forms of source documents changed without initials or dates, 7) 3 subjects had no documentation with respect to pain that qualified them for study (that actually brings the total up 5), 8) 4 subjects did not have cardiac enzymes at 8 hours and/or at 16 hours, 9) 5 subjects did not have source EKGs at the time of discharge or at 30 days.

Czech Republic: 6 items are listed which include 1) the regional coordinator who signed the form 1572 did not actively supervise nor participate in the conduct of the study, 2) sometimes, the site's sub-investigator did the case-report signing, 3) the physicians who performed study critical functions were not listed on the form 1572, 4) 4 of the 21 subjects who had clinical events did not, 5) 2 subjects enrolled in the study had no documentation of the pain, 6) for 1 subject the infusion start time could not be found.

None of this two inspections concern me at all with respect to interpreting the results of PURSUIT. It does reflect, however, upon the perceptions that Eastern Europeans have upon the requirements imposed by "FDA inspectable" controlled clinical trials. Education is in order. It also reflects on the educating capabilities of the European coordinator of the study, namely, Quintiles.

Detroit, Michigan: There is unequivocal evidence that of the patients randomized by the Detroit site, 50 of 93 patients had completely fabricated EKGs on the 30 day case report forms. For example, the 30 day EKG was a photocopy of the baseline EKG and simply had the date changed. This was discovered by the monitoring site (Duke) on a monitoring visit . The Duke monitoring unit notified COR. COR did not report that to the NDA, or if they did we are not aware of it. The Detroit site's data are in the analyses and there is no analysis that excludes the Detroit site. To my mind, that raises a serious question with regard to the validity of all of the data. What else does COR know that they are not telling?

There were no major problems found with the routine inspections of 3 sites involved in the IMPACT II study.

Inspection Summary

We understand that beginning Monday, 3/9/98, both the Duke coordinating center and COR are going to have on-site, simultaneous surprise inspections. These inspections will obtain the following information, a list of studies monitored, a list of problems found, to whom and when problems were reported and a copy of the contractual agreement between the sponsor and Duke.

Additionally, surprise visits will also be made to 3 other clinical centers that participated in the PURSUIT trial.

The Clinical Investigations Branch, Division of Scientific Investigations, HFD-344, plans to recommend that the sponsor be required to verify all other study sites to insure that the data submitted to the NDA are valid and acceptable. They will recommend that such verification be before the NDA is approved, in part depending upon their findings during the week of 3/9/98.

We cannot wait until this inspection is completed before forwarding this package to you. So, there will be further memoranda to come.

I have not brought this matter to COR's attention. Hard to surprise, if I had alerted COR or Duke by discussing the Detroit site fabrication of EKGs. I am uncomfortable with not having discussed it with either party, but the consequences are drastic and the to-be-done inspection results are critical, so it comes off without a hitch. Out of 10,948 randomized patients, there are only 73 events. Every event counts and wouldn't take too many to wreck the results.

Although letters are part of this transmittal package, it is possible that neither one will do until you have decided what to do. Similarly, the package insert will need attention, once you decide what will be approved. Chemistry, biopharmaceutics and pharmacology parts of the package insert are final and will not require attention later.

More Data to Look at

I have asked COR to provide a graphic description of the time-to-events as they relate to 1) bleeding and 2) percutaneous interventions. I hope this will give some insights into the relationship between bleeding and intervention, other than the word descriptions currently available. These analyses and CORs description of the findings are appended to this memorandum.

Summary of Summaries

From the submitted results, provided one thinks they represent the studies accurately, there is no question that eptifibatide should be approved. How to write the indications with respect to the identification of the patients who should receive treatment is a judgement call. Whatever you decide as the "best" option will be acceptable to the Division. You need not commit the reasoning to writing, from our point of view.

It is hard for me to see the reasoning that would choose any dose other than the PURSUIT "low dose". The duration of the infusion regimen depends entirely on whether the "unstable angina" claim is awarded. The infusion must be for 72 hours if "unstable angina" is to be a claim.

I see no way that we can take an action until the Detroit site and the insinuation it causes on the rest of the data is clearly settled. I am uncomfortable with issuing a "non-approval" action on the basis of the Detroit site's poor judgement. Hopefully, COR will withdraw the NDA (but we have not spoken with COR in any way about the entire problem, yet), until the matter is resolved. If we need to take an action, I would recommend "approvable, pending satisfactory resolution of....". There must be a simple explanation for what seems like a stupid error.

cc:
Orig.
HFD-110
HFD-110/CLoCicero
HFD-110/RLipicky

Attachment 3
Bleeding in the PURSUIT Study

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Bleeding in the PURSUIT Study

The following document examines the effect of eptifibatide (INTEGRILIN™) on the risk of bleeding among patients enrolled in the PURSUIT study. This includes both the effect of eptifibatide on bleeding among patients undergoing cardiac procedures and a comparison of the two eptifibatide dosing regimens used in PURSUIT.

The results of the PURSUIT study demonstrate: First, that the greatest risk of bleeding occurred in patients undergoing coronary artery bypass procedures (CABG) and that eptifibatide did not increase this risk. Second, that the incremental risk of major bleeding that is conferred by eptifibatide therapy over placebo is seen primarily among patients who have placement of a vascular access for a percutaneous cardiac procedure while on study drug. Third, that the increased risk of bleeding associated with eptifibatide therapy occurred primarily after the procedure. Fourth, that the two eptifibatide dosing regimens used in PURSUIT (a bolus of 180 μg followed by a continuous infusion of either 1.3 or 2.0 μg/kg-min) did not differ appreciably in risk of bleeding in patients who underwent PCI.

The following is a brief outline of the analyses that will be presented below:

1. Overall Study Results – TIMI Grade Bleeding
2. Bleeding Risk by Cardiac Procedure
   - Bleeding in the Proposed Indication
   - Bleeding by Cardiac Procedures
3. Timing of Bleeding in Relation to Cardiac Procedures
4. Dose Response of Bleeding in the Two Eptifibatide Regimens
5. Summary

Please note that many of these analyses, particularly those based on the specific cardiac procedures performed, should be examined with the caveat that these subgroups are defined post-randomization, and therefore do not enjoy the full protection against selection bias that randomization allows. Nonetheless, important clinical information is available from examination of these subgroups, particularly in view of the fact that the indication statement proposed by FDA is a specific subgroup of the PURSUIT patient population.

1. Overall Results – TIMI Grade Bleeding:

The incidence of major bleeding in the overall 'as treated' patient population from the PURSUIT study is displayed in the table below:

Table 1
Incidence of TIMI Bleeding in the PURSUIT Study

Bleeding Assessment	Placebo	Eptifibatide 180/2.0
Major	9.3% (425/4696)	10.8% (498/4679)
Minor	7.6% (347/4696)	13.1% (604/4679)

There was an absolute increase of 1.5% in the incidence of major bleeding and 5.5% in the incidence of minor bleeding among patients who received eptifibatide compared to those who received placebo.

2. Bleeding Risk by Cardiac Procedures:

The clinical decision to perform a cardiac procedure in an individual patient necessarily involves a risk/benefit analysis on the part of the treating physician. The relief of cardiac ischemia must be balanced against the risk of bleeding in patients receiving concomitant antithrombin (heparin) and antiplatelet (aspirin, GP IIb/IIIa inhibitors) agents. It is relevant to examine the risk of bleeding according to the procedural subgroups that account for this risk.

In many of the following analyses, reference is often made to 'early' procedures. This corresponds to the first 72 hours after randomization, the time period planned for study drug administration.

Bleeding by Proposed Indication:

On January 28, 1998 the Cardiovascular and Renal Advisory Committee recommended eptifibatide for approval in patients undergoing percutaneous comary intervention (PCI) at the time of the procedure. The following table examines the incidence of bleeding according to whether patients fit this subpopulation:

Table 2
Major Bleeding
Patients Undergoing Early PCI vs. All Others

	Placebo	Eptifibatide 180/2.0
Early (within 72 hours) PCI	4.6% (28/609)	9.7% (58/601)
No Early PCI	10.0% (397/3968)	11.0% (440/4003)

The greatest risk of bleeding occurred in the early PCI group, with an approximate doubling in the incidence of major bleeding. This increase is similar to that which was seen in the EPIC study, where the incidence of major bleeding increased from 7% in the placebo group to 14% in the abciximab bolus plus infusion group. The increased risk of bleeding with GP IIb/IIIa inihibitors can be minimized by the strict control of heparin dosing, as was seen in both the EPILOG study with abciximab and the PRIDE study (Protocol 96-023) with eptifibatide.

For comparison, the absolute decrease in the incidence of the primary endpoint was 5.0% in the early PCI subgroup (16.8% and 11.8% in the placebo and eptifibatide groups, respectively). It is important to note that more than half of this absolute difference was realized before the PCI procedure (an absolute difference of 3.7 % in the incidence of ischemic events, 5.5% in the placebo group compared to 1.8 % in the eptifibatide-treated group).

The difference in the absolute incidence of clinical events after PCI was 2.1%, from 12.4% in the placebo group to 10.3% in the eptifibatide treated group). This decrease of 2.1% would be the expected benefit if patients do not have drug started until immediately prior to PCI as recommended in the current draft indication statement. As will be seen in section 4, the risk of bleeding occurs after the procedure. Therefore, by delaying treatment with eptifibatide until the time of PCI, the current draft indication statement erodes the benefit experienced by the PCI subgroup in PURSUIT while maintaining the bleeding risk.

Finally, patients who did not undergo early PCI experienced a much smaller increase in the incidence of major bleeding, representing an absolute increase of

1% of treated patients. Therefore, there was no management strategy used in the PURSUIT study that resulted in an unacceptable bleeding risk.

Bleeding by Cardiac Procedures:

All cardiac procedures (PCI, diagnostic angiography and coronary artery bypass grafting – CABG) result in bleeding. In the case of PCI or diagnostic angiography, placement of an arterial access leads to local bleeding at the site of vessel puncture. CABG is associated with post-thoracotomy bleeding into the thorax.

In the PURSUIT study, CABG was the most frequent cause of major bleeding. The following table displays the incidence of major bleeding excluding episodes that occur after a CABG procedure:

Table 3
Incidence of non-CABG Related Bleeding

	Placebo	Eptifibatide 180/2.0
Major	2.4% (111/4577)	4.0 % (186/4604)

Therefore, most episodes of major bleeding occurred in conjunction with a CABG procedure. Among bleeding episodes not associated with CABG, patients receiving eptifibatide experienced a 1.6% increase in the incidence of major bleeding.

The following table displays the incidence of major bleeding according to the most invasive cardiac procedure performed during the period of study drug administration (i.e., within 72 hours - CABG > PCI > diagnostic angiography > none):

Table 4
Incidence of Major Bleeding by Cardiac Procedures
(CABG, PCI and Diagnostic Angiography)

Procedural Status	Placebo	Eptifibatide 180/2.0
Early CABG	62.4 % (113/181)	57.5 % (104/181)
Early PCI*	3.0 % (18/595)	8.8 % (52/590)
Early Angiography**	16.2 % (138/852)	19.4 % (168/865)
Early Angiography***	1.1% (5/466)	3.3% (16/487)
No Early Cardiac Procedures	5.3% (156/2941)	5.9% (174/2968)

*Excludes patients undergoing Early CABG
**Excludes patients undergoing Early CABG or Early PCI
***Excludes patients undergoing CABG and PCI at any time

An increased risk of bleeding among patients receiving eptifibatide compared to placebo was seen primarily among patients who underwent percutaneous procedures. The relative risk of bleeding was higher among patients who underwent PCI compared to those undergoing only diagnostic angiography. In absolute terms, the increased risk of bleeding was split relatively evenly between those undergoing PCI (34 patients) and those undergoing diagnostic angiography without a revascularization procedure (30 patients).

It is important to note that eptifibatide-treated patients who underwent early CABG and those undergoing no early cardiac procedures experienced an incidence of major bleeding very similar to that of the placebo group. In particular, eptifibatide did not increase the incidence of major bleeding in the CABG subset in spite of the fact that this subset experienced overall the highest major bleeding rate. Presumably, CABG patients did not experience an increased incidence of bleeding with eptifibatide since study drug was discontinued shortly before the CABG procedure, allowing platelet function to recover consistent with the short half-life of eptifibatide.

The following conclusions can be drawn from the analysis of bleeding risk by cardiac procedures:

- CABG-related bleeding accounted for the majoritiy of major bleeding events.
- There were fewer CABG-related major bleeding events among eptifibatide treated patients compared to placebo.
- In patients who underwent early PCI or diagnostic angiography, there was an increase in major bleeding among patients receiving eptifibatide compared to placebo.

- Patients undergoing no early cardiac procedures who received eptifibatide experienced an absolute increase in the incidence of major bleeding of 0.6%.

4. Timing of Bleeding in Relation to Cardiac Procedures:

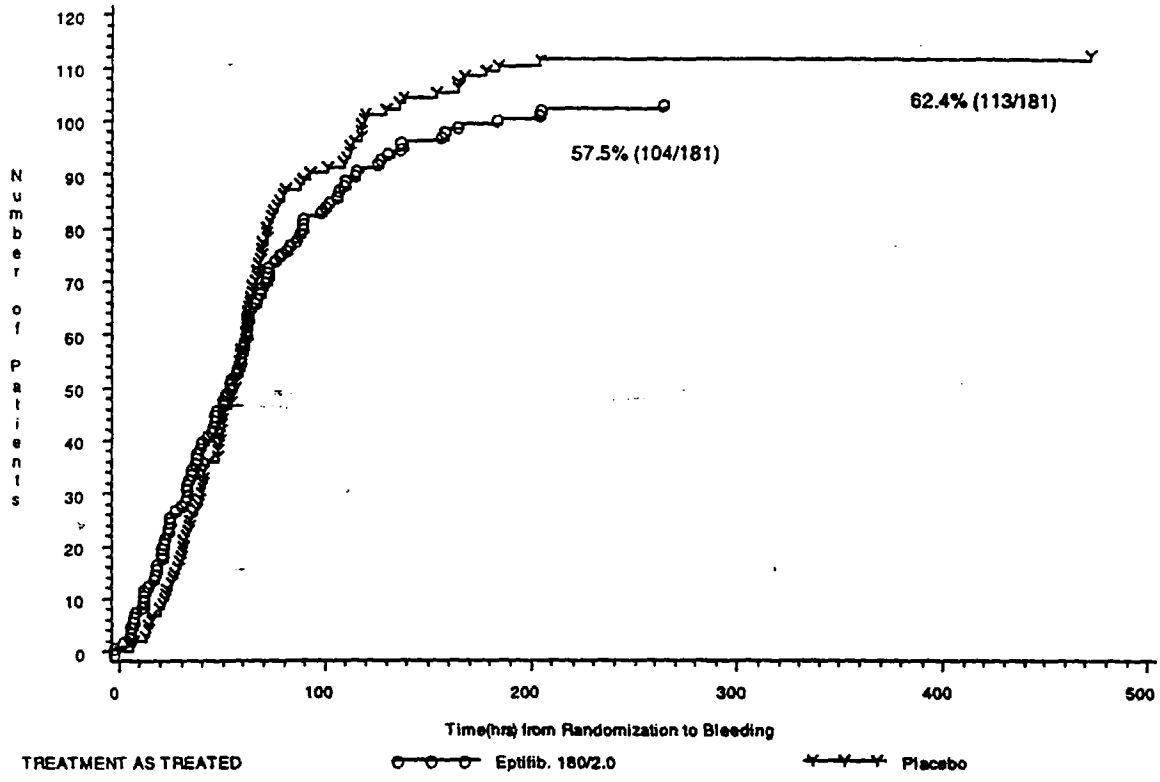
Analysis of the onset of bleeding in relation to cardiac procedures is of interest in that it provides useful information to the clinician that allows one to manage risk. Specifically, the following analyses examine the onset of major bleeding in relation to cardiac procedure within each subgroup. The 'onset of bleeding' is defined as the time of the finding that resulted in the categorization of a bleeding event as 'major'. The onset of bleeding is presented in two ways: time from enrollment (Figures 1,3,5,7 and 9) and time from procedure (Figures 2,4, 6 and 8). Please note these are step functions, representing patient events, and not Kaplan-Meier curves. No censoring has been performed in these graphs.

Early CABG

The following figures (1 & 2) display the step function of bleeding as a function of time:

Figure 1

Time (hrs) from Randomization to TIMI Major Bleeding
Patients Undergoing CABG within 72 Hours



* Times could not be estimated for a small number of patients

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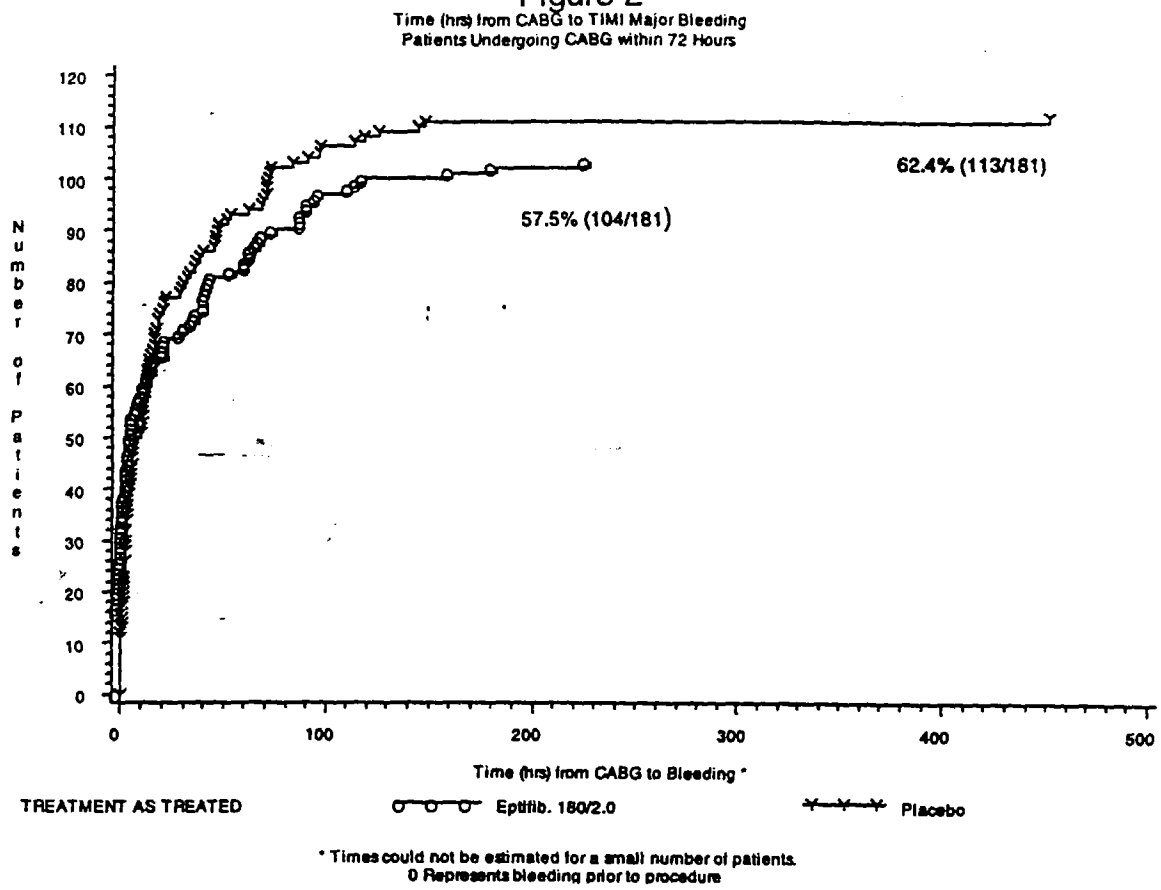
Figure 2



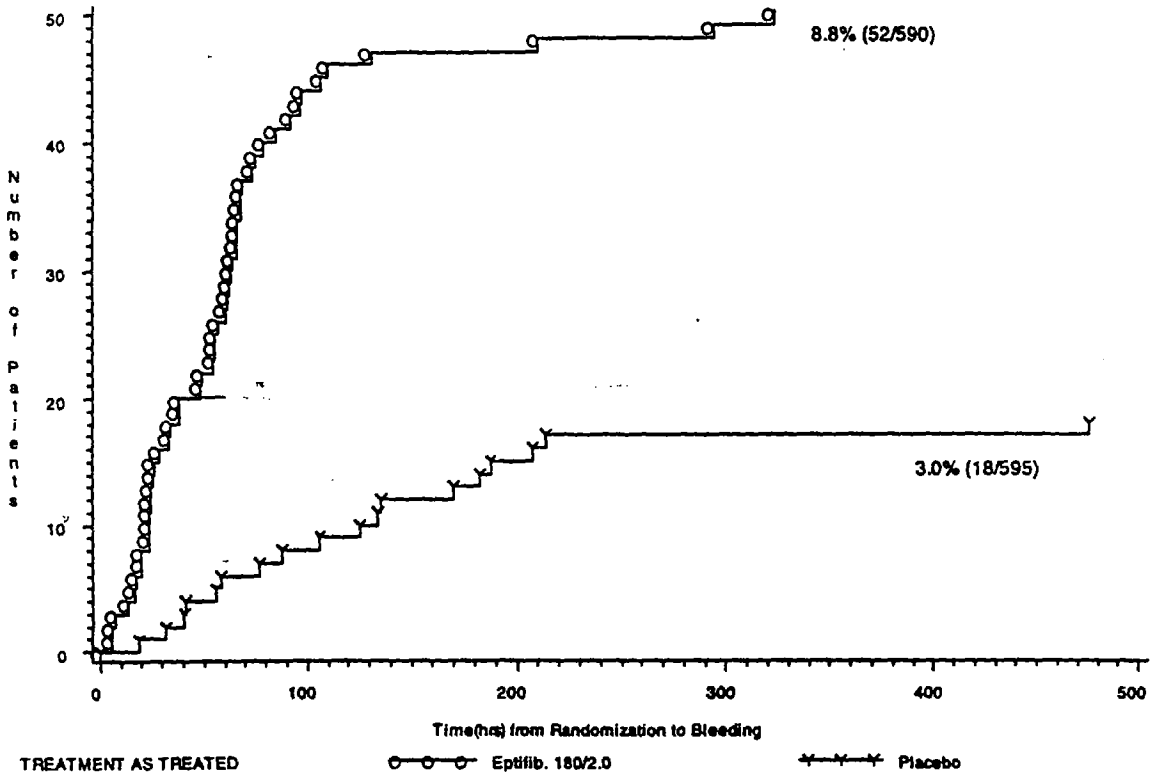
Both figures show little difference in the onset of bleeding events between the eptifibatide and placebo groups. Thus, as the point estimate at 30 days suggests, there was no increased risk of bleeding in eptifibatide-treated patients who undergo CABG.

Early PCI

The following figures (3 & 4) display the step function of bleeding as a function of time in patients who undergo early PCI. This analysis excludes patients who also underwent CABG within 72 hours.

Figure 3

Time (hrs) from Randomization to TIMI Major Bleeding
Patients Undergoing PCI but Not CABG within 72 Hours



* Times could not be estimated for a small number of patients

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Figure 4

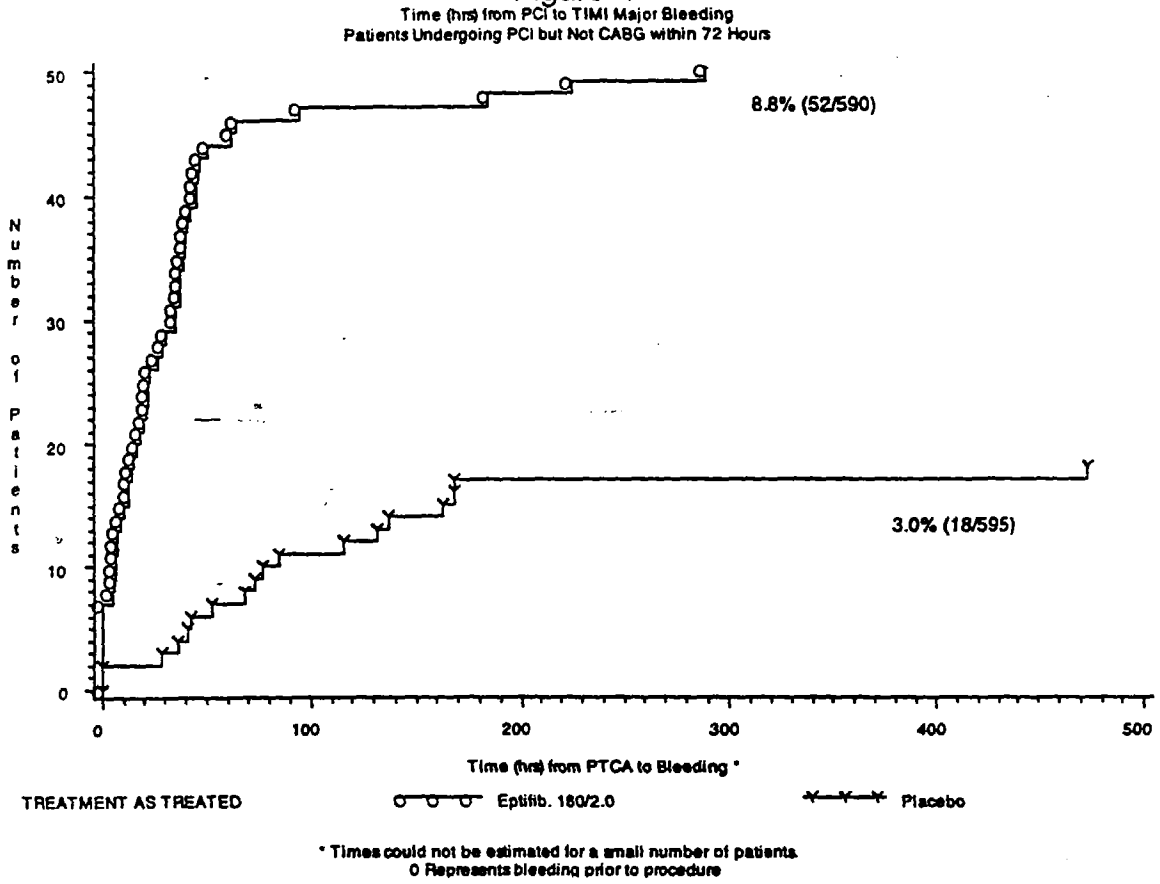


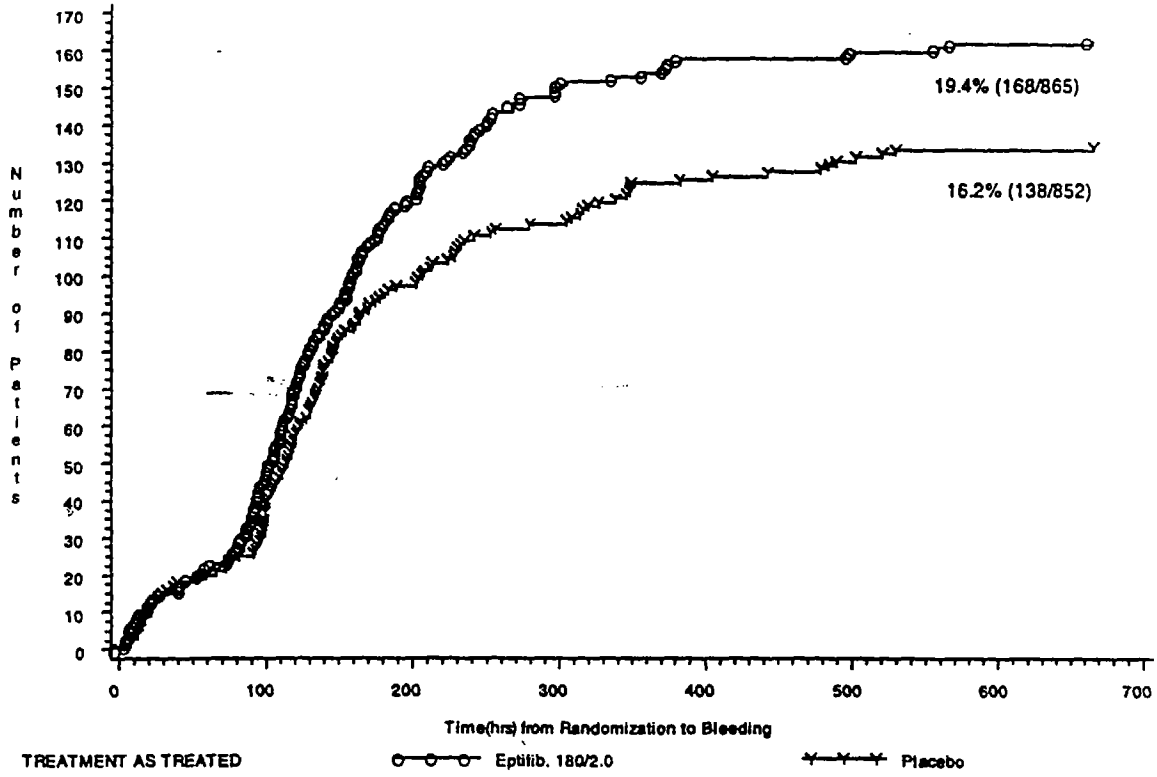
Figure 3 demonstrates a higher incidence of major bleeding in patients that underwent early PCI who received eptifibatide compared to placebo. It is important to note that most of the bleeding occurred after the PCI procedure. Specifically, there were 7 patients in the eptifibatide group who experienced major bleeding before PCI compared to 2 in the placebo group (Figure 4). Most of the increment in bleeding in eptifibatide treated patients occurred after the PCI procedure.

Early Angiography

The following analyses (Figures 5 & 6) displays the step function of bleeding from time of enrollment and time of angiography in those patients who undergo diagnostic angiography, excluding those who also undergo early CABG or PCI.

Figure 5

Time (hrs) from Randomization to TIMI Major Bleeding
Patients Undergoing Angiography, but not PCI or CABG, within 72 Hours



* Times could not be estimated for a small number of patients.

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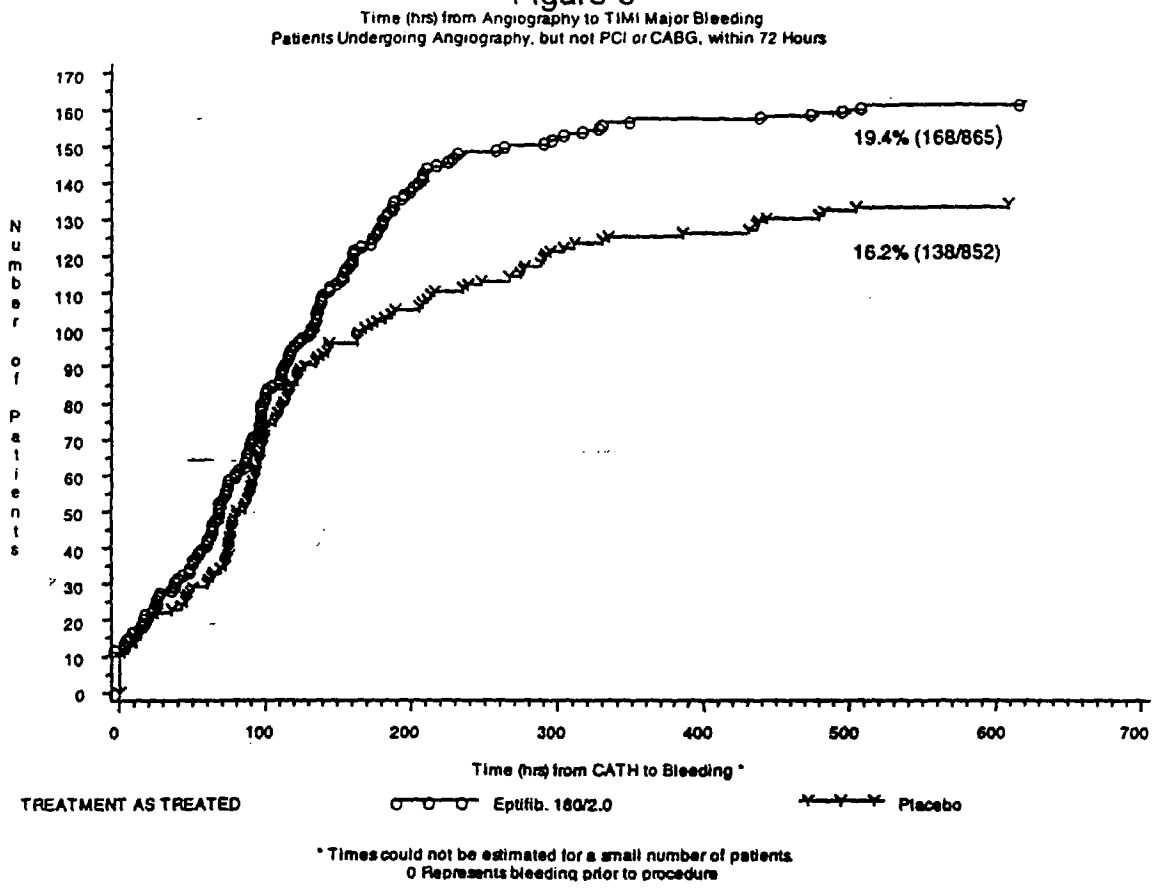
Figure 6

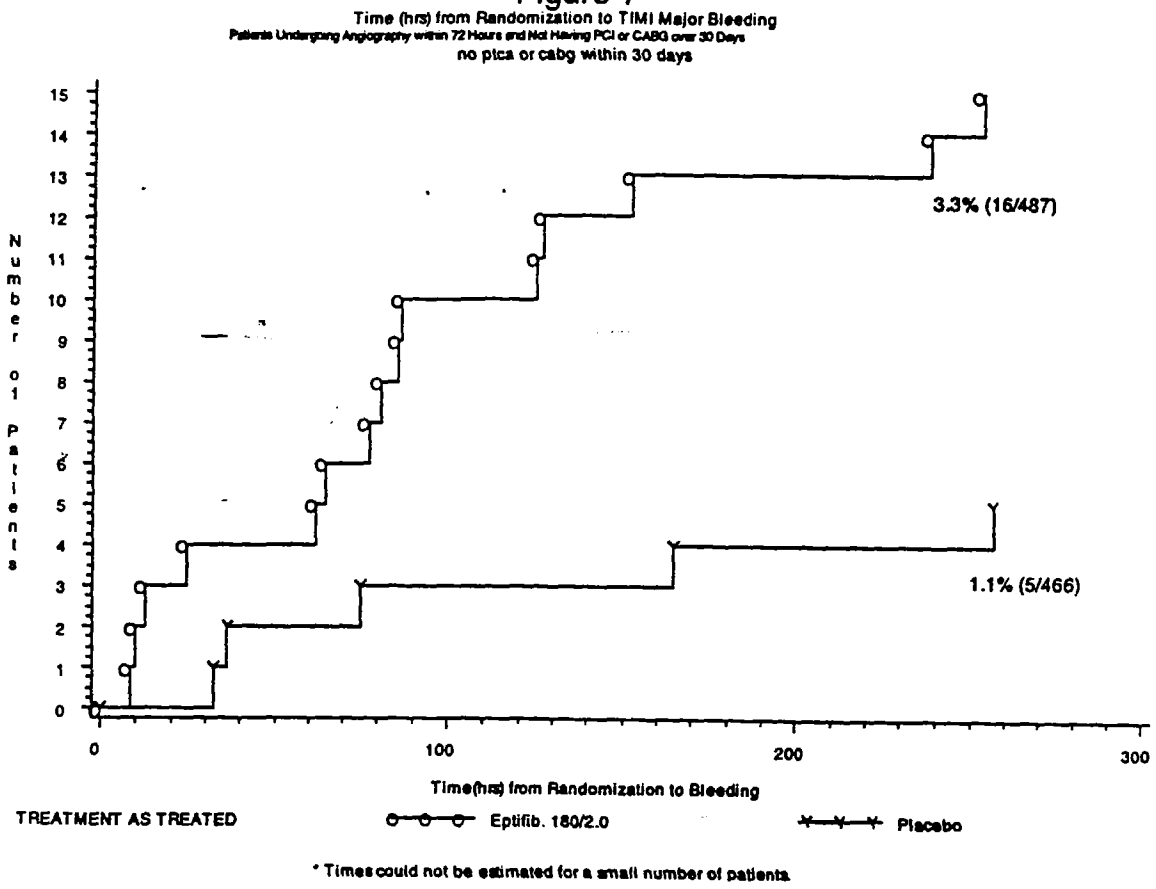


Among patients who underwent early angiography, those who received eptifibatide experienced more bleeding than patients who received placebo. The greatest difference between the treatment groups appears to occur relatively late in the therapeutic course, towards the end of the infusion (after 130 hours). It is particularly important to note that there was no increased risk of major bleeding before angiography in this subgroup (Figure 6).

The late risk of bleeding in the eptifibatide-treated subgroup undergoing early diagnostic angiography compared to placebo is unexpected because the risk of bleeding is remote from study drug administration. The explanation of this is that there appears to be a differential number of patients receiving eptifibatide compared to placebo who underwent cardiac procedures after 72 hours. Presumably, patients who received placebo underwent a greater number of revascularization procedures in the immediate post-acute (appx. 72 hour) period (these, of course, are associated with a higher incidence of major bleeding). The situation becomes clearer when the patients undergoing late (post-72 hours) PCI and CABG procedures are excluded and when one analyzes only the early angiogram group who underwent no subsequent procedures during the rest of

the study period for bleeding. The following figures (7 & 8) display the incidence of major bleeding when all patients undergoing CABG and PCI (not just early procedures) are eliminated.

Figure 7



* Times could not be estimated for a small number of patients.

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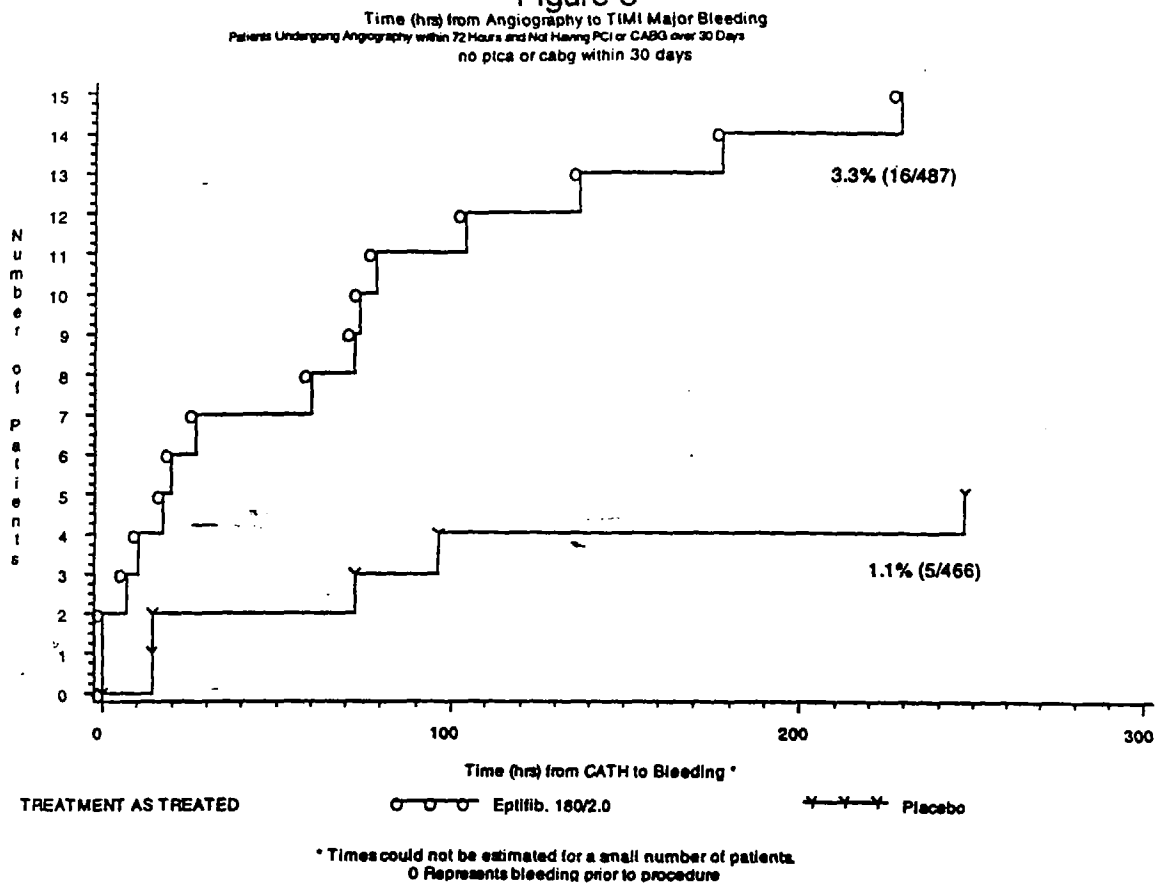
Figure 8

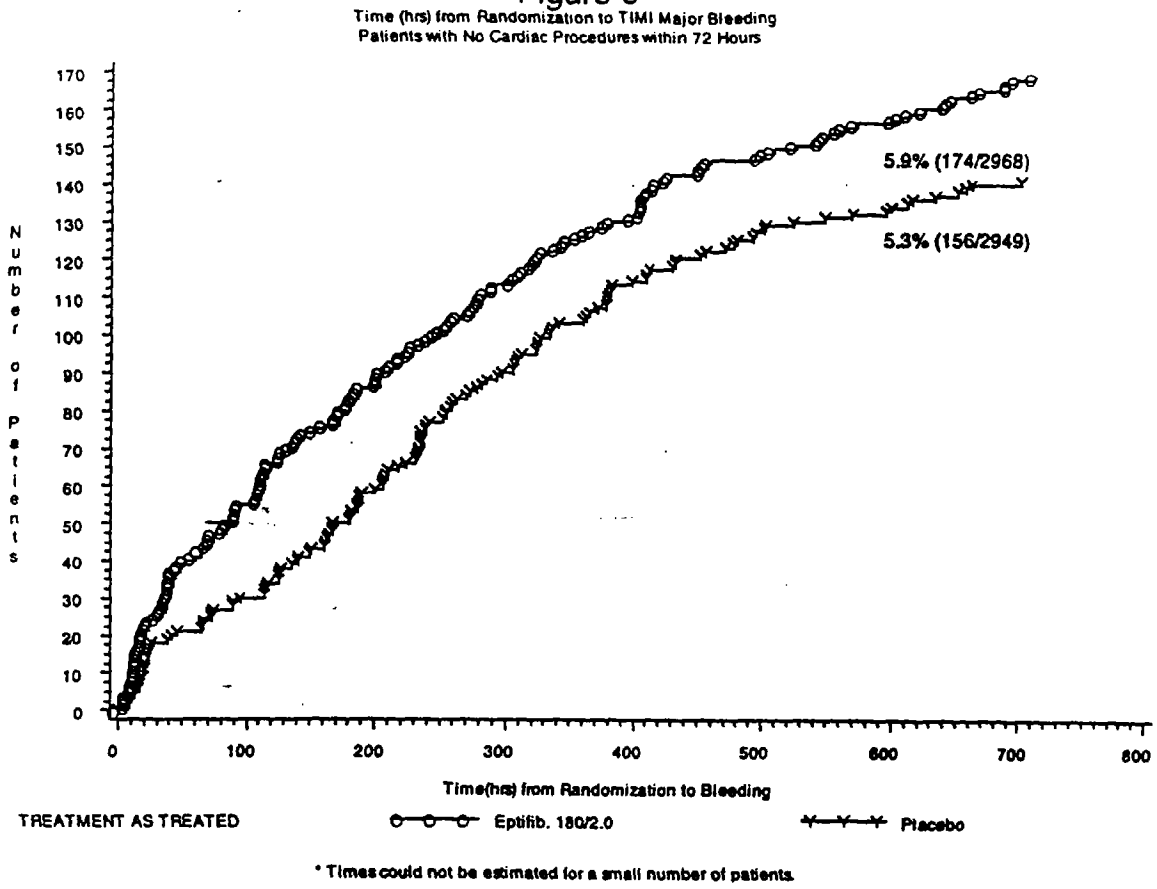


In this subgroup, there is an incremental risk of bleeding among patients receiving eptifibatide compared to placebo (5 patients in the placebo group compared to 16 in the eptifibatide treated group) during the period of study drug administration.

No Cardiac Procedures

Figure 9 displays the step function of major bleeding in patients who undergo NO early procedures and excludes patients who undergo angiography , PCI or CABG during that time.

Figure 9



* Times could not be estimated for a small number of patients.

Early in the infusion course, eptifibatide treated patients who underwent no early cardiac procedures experienced a similar incidence of bleeding compared to the placebo group. The incremental risk of bleeding among patients treated with eptifibatide represents ~ 0.57% of patients, and is relatively constant over time.

In conclusion,

- The time course of bleeding in association with CABG is unaltered by therapy with eptifibatide.
- Little bleeding occurred prior to cardiac procedures.
- Most of the increment in bleeding events among patients receiving eptifibatide occured after a percutaneous cardiac procedure.
- Patients who underwent diagnostic angiography experienced a greater risk of bleeding with eptifibatide that occurred after the acute presentation.
- Patients who underwent no cardiac procedures experienced a minimal increment in bleeding.

Therefore, eptifibatide can be administered upon presentation to patients with unstable angina with little risk of bleeding prior to a cardiac procedure.

4. Dose Response in Bleeding of the Two Eptifibatide Regimens:

In your draft indication statement, the 180/1.3 dosing regimen is recommended for approval in patients undergoing PCI. Therefore, an examination of the eptifibatide dosing regimens used in PURSUIT for a possible dose response in major bleeding was made by analysing patients who underwent early PCI and who were enrolled at the time the lower dose of eptifibatide was dropped – the 'contemporaneous analysis': This subgroup is important to the investigation of relative bleeding risk because in the overall study, patients undergoing early PCI experienced the greatest relative increase in bleeding between eptifibatide and placebo. Therefore, this subgroup is the most sensitive indicator of bleeding risk.

Table 5
Incidence of TIMI Bleeding in Patients Undergoing Early PCI
(Excludes Patients Undergoing CABG)

TIMI Grade	Placebo	Eptifibatide 180/1.3	Eptifibatide 180/2.0
Major	3.8% (7/184)	7.9% (14/177)	8.5% (16/188)
Minor	10.3% (19/184)	19.8% (35/177)	18.1% (34/188)

It is apparent from this analysis that the bleeding risk between the two eptifibatide-treated groups was similar. Therefore the recommendation of the 1.3 infusion regimen rather than the 2.0 µg/kg-min infusion regimen is not supported by safety data within the PURSUIT study for patients undergoing PCI. These data together with the efficacy analysis (cf. Attachment 2) that shows a greater benefit for the 180/2.0 regimen in the 'contemporaneous analysis' indicates that this should be the recommended dose.

5. Summary

- Patients undergoing CABG had the highest overall risk of major bleeding and made the greatest contribution to the overall bleeding rates in the PURSUIT study
- Eptifibatide did not increase risk of bleeding among patients undergoing CABG.
- When CABG related bleeding is subtracted from the overall bleeding rates, the incidence of major bleeding was 2.4 (111/4577) and 4.0% (186/4604) in the placebo and eptifibatide-treated groups, respectively.
- The greatest increment in bleeding among eptifibatide-treated patients is experienced by patients undergoing early PCI (18/595 and 52/590 in the placebo and eptifibatide 180/2.0 groups, respectively, an absolute increase of 5.8%). The increased incidence occurs primarily after the PCI procedure, but a benefit in clinical events was evident both before and after the PCI procedure.
- Patients receiving eptifibatide who underwent diagnostic angiography without a revascularization procedure and patients who did not undergo any cardiac procedures experienced a minimally increased risk of major bleeding compared to placebo.
- All of our analyses indicate that treatment with eptifibatide prior to cardiac procedures contributed little to the risk of bleeding. The majority of benefit was accrued during the preprocedural period in the early PCI subgroup, however.
- None of our analyses have identified the 72 hour infusion duration as an important factor in determining bleeding risk. The 72 hour infusion duration provides benefit until a patient can be evaluated for a revascularization procedure. Since patients presenting with an acute coronary syndrome are at greatest risk for an ischemic event during the first 72 hours after presentation or are triaged to a revascularization procedure within this time frame, the 72 hour infusion represents an appropriate duration.
- The recommendation of the 180/1.3 dosing regimen is not supported by the safety data among patients undergoing early PCI, the group at highest risk of bleeding due to drug therapy. The 2.0 and 1.3 infusion regimens cause a similar increment in bleeding risk compared to placebo.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-718

MAR 21 1997

COR Therapeutics, Inc.
Attention: Ellen L. Martin
Director, Regulatory Affairs
256 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Martin:

Please refer to your new drug application dated April 1, 1996, received April 2, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Integrilin™ (intrifiban) Injection.

We acknowledge receipt of your submissions dated April 4 and 22, 1996; May 7, 15, and 30, 1996; June 10 (2 documents), 14, and 26, 1996; August 2 and 8, 1996; October 8, 15, 22, and 30, 1996; November 13 and 21, 1996; December 20, 1996; February 6 and 21, 1997. The User Fee goal date for this application is April 2, 1997.

This application provides for the administration of Integrilin as an adjunct to Percutaneous Transluminal Coronary Angioplasty (PTCA) for the prevention of acute cardiac ischemic complications related to abrupt closure of the treated coronary vessel.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely yours,

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CSO Review of Final Printed Carton and Vial Labeling
NDA 20-718

Date of Amendment: May 13, 1998

Date of Review: May 18, 1998

Applicant Name: COR Therapeutics, Inc.

Product Name: Integrilin (eptifibatide), 20 mg/10 ml and 75 mg/100 ml Injection

Evaluation:

The final printed labeling submitted on May 13, 1998 is not identical to the carton and vial labeling that accompanied the approveable letter of April 1, 1998. However, Dr. Ali Al-Hakim from HFD-180, the reviewing chemist, has reviewed the final printed labeling and found it acceptable. Please refer to his review of the final printed labeling.

Recommendation: —
An approval letter should issue for this NDA.

Colleen LoCicero, CSO

cc: Orig. NDA
HFD-110
HFD-110/LoCicero
HFD-110/SBenton

APPEARS THIS WAY
ON ORIGINAL

RHPM Overview of NDA 20-718
Integrilin (eptifibatide) Injection 20 mg/10 mL and 75 mg/100 mL
February 11, 1998
Updated May 18, 1998

Type: 1 P

Date of Application: December 3, 1996
Not approved: March 21, 1997
Major Amendment: September 30, 1997
User Fee Goal Date: April 1, 1998
User Fee Goal Date After the Approvable Letter: July 15, 1998

Background
The NDA for Integrilin was submitted on April 1, 1996 and provided for the administration of Integrilin as an adjunct to Percutaneous Transluminal Coronary Angioplasty (PTCA) for the prevention of acute cardiac ischemic complications related to abrupt closure of the treated coronary vessel. Impact II (protocol #93-014) was the only major study submitted in support of this application. This application was presented to the Cardiac and Renal Drugs Advisory Committee on February 28, 1997. The Committee concluded that the Impact II study alone was not sufficiently robust to support approval even though the study indicated that the drug had activity. A not approvable letter issued on March 21, 1997. This application was transferred from HFD-180 to HFD-110 in May 1997. A major amendment was submitted on September 30, 1997 and provides for the following indications: 1) Prevention of death and myocardial infarction (MI) in patients with unstable angina or non Q-wave MI; 2) Adjunct to percutaneous transluminal coronary angioplasty (PTCA) for the prevention of abrupt closure of the treated coronary vessel.

Cardiovascular and Renal Drugs Advisory Committee - January 28, 1998
The committee met again to review the results from two clinical trials, IMPACT II and PURSUIT. The committee recommended that Integrilin be approved for use in patients undergoing intervention (PTCA). Five member voted for the restricted use, 1 favored broader use and there was one abstention. The recommendation was based on the conclusion that the results of PURSUIT confirmed those of IMPACT II. Use and dose should be limited to the IMPACT II results. Concerns were expressed about increased bleeding seen in PURSUIT. More data would be needed to approve use in acute coronary syndrome.

Division Director Memo
In his memo dated March 10, 1998, Dr. Lipicky recommended that Integrilin be approved pending resolution of the Detroit site inspection issue.

Medical Reviews
In his review dated February 17, 1998, Dr. Hammond recommended that Integrilin not be approved based on the PURSUIT data alone. Consideration may be given to whether the PURSUIT study supports the IMPACT II study and whether the data from the two studies together support approval of the drug. Dr. Hammond had no labeling changes.

Statistical Review
In his review dated December 22, 1997, Dr. Nuri concluded that the PURSUIT trial seemed to support the sponsor's claim that integrilin has significantly reduced the event rate of MI or death over placebo (within 30 days of treatment) in patients with unstable angina or non-Q wave myocardial infarction.

Biopharmaceutical Review
In her review dated March 5, 1998, Dr. Parekh concluded that the biopharmaceutical data were acceptable. Her labeling comments have been added to the draft labeling.

Pharmacology Review
In his review dated February 17, 1998, Dr. Resnick addresses the impurity/degradant issue raised by the Chemists in HFD-180. He concluded that none of the degradation products at issue have been adequately evaluated for mutagenic or clastogenic potential. Clinical trials experience cannot substitute for this omission.

In his review dated January 5, 1998, Dr. Resnick recommended following Dr. Choudary's labeling mark-up that Dr. Resnick has modified; the changes have been added to the draft labeling.

Chemistry Review
In his reviews #2 and #3 both dated February 19, 1998, Dr. Al-Hakim concluded that the drug product stored under refrigerated conditions is acceptable; the drug product stored at room temperature has too high This issue was communicated to COR in a February 19, 1998 telecon.

The methods have not been validated, therefore, the methods validation paragraph has been added to the approval letter.

EER - Acceptable November 4, 1997

Environmental Assessment: See Environmental Assessment dated August 20, 1996. In their resubmission, the firm requested a categorical exclusion for environmental assessement in accordance with the Final Rule dated July 29, 1997 (21 CFR, Section 25.25(d) - Federal Register, Vol. 62, No. 145, pages 40570-40600, 21 CFR, Part 10).

Trademark - The Labeling and Nomenclature Committee found the name "Integrilin" to be acceptable on May 23, 1996.

Chemist labeling comments have been added to the draft labeling.

Microbiology Review
In his review dated November 13, 1997, Dr. Stinavage recommended that the application be approved with regard to sterility assurance.

DSI
CIB received information of possible fraud from the field inspector in Detroit regarding the investigation of that site. Since all three sites have problems, Dr. El-Hage recommended that the application not be approved until the data from all the U.S. study sites are verified.

RHPM Summary

1. The site inspection issues have been resolved.

2. To my knowledge there are no outstanding issues that might prevent action on this application.

Zelda McDonald, RHPM

cc: Orig. NDA
HFD-110
HFD-111/McDonald

RHPM Overview of NDA 20-718
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CSO Summary

1. Other than labeling changes and resolution of the site inspection issues,to my knowledge there are no other outstanding issues that might prevent action on this application.

2. See attached comments regarding labeling from Ms. Norden, DDMAC. In response to Ms. Norden's first comment, Dr. Hammond recommended adding Table 8-46 from study #94-016; it has been added to the draft labeling.

cc: Orig. NDA
HFD-110
HFD-111/McDonald

Zelda McDonald, RHPM