CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-718

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV - 7 1997

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

RE: NDA# 20-718
Integrilin (eptifibatide)
MACMIS ID# 5843

Dear Ms. Martin:

Reference is made to COR Therapeutics, Inc.'s (COR) letter dated October 9, 1997, which was in response to a letter from the Division of Drug Marketing, Advertising and Communications (DDMAC), dated September 25, 1997. DDMAC's letter concerned a journal ad that promoted Integrilin (eptifibatide) in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, this journal ad promoted an unapproved new drug.

In your letter, you explained that you have discontinued use of this journal ad, and that similar materials have been discontinued and destroyed. In addition, you described that you will carefully review future materials to ensure that they comply with the regulations.

In addition, in your letter, you stated that there was no intent to advertise, prior to its approval, the use of or to make claims of safety and efficacy of Integrilin. You also stated that the purpose of the journal ad was to inform the medical community about COR's research in the area of platelet-mediated thrombosis and its possible relationship to unstable angina and, therefore, was consistent with the pre-approval promotion guidelines for institutional advertisements.

DDMAC has reviewed COR's arguments and has the following comments. DDMAC notes that the focus of the advertisement was the suggestion that a therapy founded on broad-based inhibition of platelet aggregation would diminish morbidity and mortality in patients with unstable angina. The focus was not on COR, its attributes as a company or its commitment to research in the area of antiplatelet therapy that could be a general theme for an institutional advertisement. The journal ad made claims for the product (Integrilin), including its mechanism of action (i.e., inhibition of platelet aggregation) and its intended uses (i.e., diminish morbidity and mortality in patients with unstable angina). Therefore, DDMAC

maintains its position that the journal ad was not an institutional advertisement, but promotion of an unapproved new drug.

Lastly, COR requested a discussion with DDMAC concerning promotional issues. If COR chooses, proposed promotional materials may be submitted to DDMAC prior to dissemination with a request for comment. Promotional materials should be directed to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. For your review, copies of the Pre-Approval Promotion Guidance and the Guidance to Expedite the Review of Launch Campaign Submissions are enclosed. These guidance documents are currently being revised as described in the enclosed Federal Register, dated March 28, 1997.

If COR believes that a meeting with DDMAC is necessary, it should submit a written request to DDMAC for consideration. The written request should include a proposed agenda, a listing of planned attendees representing COR, a listing of requested participants from the Center for Drug Evaluation and Research (CDER), and the appropriate time at which supporting documentation for the meeting will be sent to DDMAC. Please note that all supporting documentation should be received by DDMAC at least two weeks in advance of the meeting. A copy of the Manual of Policies and Procedures for Formal Meetings Between CDER and CDER's External Constituents is enclosed for your information.

In light of the actions taken by COR in discontinuing these materials, DDMAC considers this matter closed. If you have any further questions or comments, please address them to the undersigned at the address listed above. DDMAC reminds COR that only written communications are considered official.

In all future correspondence regarding this particular matter please refer to MACMIS ID #5843 in addition to the NDA number.

Sincerely,

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

HFD-110/McDonald

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

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

SEP 25 1997

RE: **NDA# 20-718**
Integrilin (intrifiban)
MACMIS ID #5843

Dear Ms. Martin:

As part of its routine monitoring activities, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of a COR Pharmaceuticals, Inc.'s (COR) journal advertisement regarding Integrilin (intrifiban) and the PURSUIT Trial. DDMAC has determined that this advertisement is in violation of the Federal Food, Drug, and Cosmetic Act (Act) and regulations promulgated thereunder. Specifically, this product promotes an unapproved new drug.

The regulations promulgated pursuant to the Act at 21 CFR 312.7 state, among other things, that an investigational new drug may not be promoted as being safe and effective for the uses under investigation. Therefore, DDMAC usually considers pre-approval promotion of drug products to be violative. However, DDMAC has traditionally recognized two methods in which sponsors may discuss products under FDA review, without making promotional claims of safety or efficacy that are prohibited by the Act.

The first method of permissible pre-approval promotion is "institutional promotion." Institutional advertisements state that a particular drug company is conducting research in a certain therapeutic area. The advertisement may not suggest any particular drug by name (proprietary or established) or otherwise suggest that a particular drug will soon be approved for use in the therapeutic area under discussion.

The second method of permissible pre-approval promotion is "coming soon" advertisements. Coming soon advertisements announce the name of a new product that will be available soon, but do not make written, verbal, or graphic

representations or suggestions concerning the safety, efficacy, or intended use of the product.

This advertisement is not considered an institutional advertisement because it makes several representations about the product including its specific use in reducing morbidity and mortality associated with unstable angina. Specifically, the journal ad makes implied claims that the PURSUIT Trial will demonstrate that Integrilin will decrease mortality and morbidity in patients with unstable angina. Although the ad does not mention Integrilin by name, there is a clear association with Integrilin by COR's dissemination of the journal ad and COR's description of possible uses and mechanism of action for the product. For example, the journal ad states:

> Steadily increasing evidence implicates arterial thrombosis resulting from platelet aggregation as a pivotal contributor to the morbidity and mortality associated with unstable angina. This suggests that, by helping to prevent arterial thrombus formation, a therapy founded on broad-based inhibition of platelet aggregation should diminish morbidity and mortality in patients presenting with unstable angina.

COR should immediately discontinue use of this journal ad and other promotional materials that are similarly violative. Please respond in writing by October 9, 1997, with your intent to comply with the above. Address your response to the undersigned at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds COR that only written communications are considered official.

In all future correspondence regarding the issues raised in this letter, please refer to MACMIS ID # 5843 in addition to the NDA number.

Sincerely,

Janet M. Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

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

NDA 20-718

-- -8 1996

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

Dear Ms. Martin:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Integrilin™ (intrifiban) Injection

Therapeutic Classification: Standard

Date of Application: April 1, 1996

Date of Receipt: April 2, 1996

Our Reference Number: 20-718

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 1, 1996, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Julieann DuBeau
Consumer Safety Officer
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-718
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau 4/8/96
DISTRICT OFFICE
JD/April 8, 1996 (drafted)
JD/4/8/96/c:\wpfiles\nda\20718604.0jd

ACKNOWLEDGEMENT (AC)

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 10, 1997

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Not Approvable Recommendation for Integrilin

TO: NDA 20-718

The sponsor presented one major study in support of the efficacy of Integrilin, a IIb, IIIa platelet inhibitor, to prevent acute ischemic events related to abrupt closure of treated coronary vessel during PTCA. That study, Impact II, randomized 2 doses of Integrilin versus placebo. It should be noted that the two Integrilin doses were very similar, differing slightly in the infusion dose (0.5 ug/kg/min versus 0.75 ug/kg/min each given for 20-24 hours). In each active arm a bolus dose of 135 ug/kg was also given. It would not be expected that there would be much difference between the doses in the effect on platelet aggregation. It should also be noted that post-infusion the anti-aggregatory effect on the platelets is reversed in 2-4 hours.

According to the statistical review,

"The primary objectives of this study are

1) to determine the efficacy of two different dosing regimens of Integrilin versus placebo in patients undergoing coronary angioplasty in reducing the incidence of death, MI, and need for urgent or emergency coronary revascularization in the first 30 days following enrollment, and

2) to determine the safety of Integrilin when used in patients undergoing coronary angioplasty.

The primary efficacy endpoint is a <u>composite endpoint</u> consisting the first occurrence of any one of these three events: <u>all cause mortality</u>, <u>myocardial infarction</u> and <u>urgent or emergency coronary revascularization.</u> Evidence of clinical benefit was to be assessed by comparing treatment groups with respect to this composite endpoint at 30 days after randomization. For this endpoint, death is defined as all-cause mortality where cause of death was to be adjudicated by an independent primary endpoint

committee."

The statistician describes the proposed statistical analysis methods as follows:

"The purpose of the primary analysis (as per protocol amendment) was to assess whether a significant difference exists in the incidence of the primary composite clinical endpoint between the placebo arm and either or both of the Integrilin arms. The primary efficacy endpoint analysis was to be performed after an adjudication of outcome events by a Clinical Events Committee (CEC). This analysis was to be based on all randomized patients (i.e., on an intent-to-treat [ITT] patient population). The planned analysis was pairwise comparisons of high and low doses of integrilin to placebo using chi-square analysis method.

To guard against inflation of the nominal .05 significance level due to multiple comparisons, a reduced (per-comparison) significance level of <.035 was planned (as per 12/03/93 protocol amendment; original protocol specified a Bonferroni adjusted α-level of .017). Integrilin effectiveness was claimed if either of the control vs Integrilin pairwise tests were significant. Thus the postulated significance levels at each of the two planned interim analyses were .00007 (for the first) and .0074 (for the second). To supplement the efficacy comparisons at the interim analyses, the (amended) protocol indicated that conditional power calculations based on the data observed to that point and the hypothesized treatment differences were to be provided to the Data Safety Monitoring Committee (DSMC) for use in monitoring the adequacy of the target sample size.

Note that no statistical rationale is given (by the sponsor) for choosing the adjusted (per-comparison) α-level of .035 as an appropriate upper bound for declaring statistical significance. This adjusted significance α-level, however, seems to correspond to a Tukey, Ciminera and Heyes (TCH) adjusted significance α-level [$.0350=1-(1-.05)^{1/\sqrt{2}}=1-(.95)^{.7071}$] for two "highly correlated" comparisons [See Tukey, Ciminera & Heyes: Biometrics (1985), 295-301], or to any correlation based multiple endpoint adjustment (ad-hoc) method [see Dubey/Armitage & Palmar: Proceedings of the VIth/XIIth International Biometrics Conference (1985/1986)] upon assuming a between treatment comparison correlation coefficient of 0.5 [under the null hypothesis, see Dunnett & Tamhane: JASA (1993); 162-170]. Note that by assuming an equi-correlation coefficient if 0.5, the average correlation coefficient is also 0.5, and the TCH and ad-hoc methods yield equivalent adjusted

significance levels.

Note also that simulation results have shown that both of these adjustment methods lead to inflation of the Type I error rate, as can be seen from the results in **Table 1** below. For two comparisons with (an assumed common) correlation coefficient of 0.5 between comparisons, the table below summaries the simulated overall (attained) Type I error rates and the simulated per-comparison α-levels for given nominal α-levels for these two methods. For comparison purpose, corresponding simulation results for the Hochberg method are also provided. The table values are based on 100,000 normally simulated variates from a two treatment group clinical trial with 100 patients per treatment group. From these table values we note that a per-comparison α-level of .035 would lead to an overall α-level of .064 and not the .05 nominal level. To maintain the nominal .05 significance level, the per-comparison α-level (prior to adjustment for interim analyses) should be $\leq$ .277, and not $\leq$.035 as proposed by the sponsor.

Table 1/ Overall Type I Error Rate Protection for Equally Correlated Two Comparisons w/ρ=.5

	Dubey/Armitage et al			Tukey et al			Hochberg		
Specified Nominal α-Level	.05	.039	.035	.05	.039	.035	.05	.039	.035
1st Per-comparison α-Level	.035	.028	.024	.035	.028	.027	.028	.022	.020
2nd Per-comparison α-Level	.035	.027	.024	.035	.027	.024	.028	.022	.020
Overall Attained α-Level	.064	.051	.046	.064	.051	.046	.047	.037	.033

(See Sankoh, Huque & Dubey, "Some comments on frequently used multiple endpoint adjustment methods in clinical trials": Submitted to *Stats in Medicine*)

Given that these technical considerations are discussed in such detail, it is reasonable to suspect that the 30 day result was not very robust. The statistician's table of both the 30 day, 24 and 48 hour results for the ITT population are provided below.

Table 4/ Sponsor's ITT Analysis Results at 24- and 48- Hour and the Primary 30-Day Time points

Endpoint	At 24-Hour Time point			At 48-Hour Time point			At 30-Day Time point		
	Event (%)	OR (%Diff)	2-Sided* P-value	Events (%)	OR (%Diff)	2-Sided* P-value	Events (%)	OR (%Diff)	2-Sided* P-value
Composite: Placebo	123 (9.6)	Pla vs	Pla vs	131(10.2)	Pla vs	Pla vs	149(11.6)	Pla vs	Pla vs
Integrilin High	89 (6.9)	.70 (2.7)	.014(.023)	102 (7.9)	.76(2.3)	.053(.063)	128(10.0)	.84 (1.6)	.201(.212)
Integrilin Low	86 (6.6)	.67 (3.0)	.006(.011)	99 (7.6)	.73(2.6)	.021(.035)	118 (9.1)	.76 (2.5)	.041(.050)
Death: Placebo	1 (0.1)	Pla vs	Pla vs	4 (0.3)	Pla vs	Pla vs	14 (1.1)	Pla vs	Pla vs
Integrilin High	1 (0.1)	1.0 (0.0)	1.00 (.913)	5 (0.4)	1.3 (-.1)	1.00(.928)	11 (0.9)	.78 (0.2)	.687 (.631)
Integrilin Low	0 (0.0)	UD(0.1)	.237 (.714)	1 (0.1)	.25 (0.2)	.367(.444)	6 (0.5)	.42 (0.6)	.108 (.175)
MI: Placebo	90 (7.0)	Pla vs	Pla vs	95 (7.4)	Pla vs	Pla vs	106(8.2)	Pla vs	Pla vs
Integrilin High	66 (5.1)	.72 (1.9)	.056(.069)	75 (5.8)	.78 (1.6)	.130(.146)	90 (7.0)	.84 (1.2)	.263(.275)
Integrilin Low	71 (5.5)	.77 (1.6)	.141(.158)	77 (5.9)	.79 (1.5)	.155(.174)	86 (6.6)	.79(1.6)	.131(.152)
Urgent CABG: Placebo	28 (2.2)	Pla vs	Pla vs	30 (2.3)	Pla vs	Pla vs	36 (2.8)	Pla vs	Pla vs
Integrilin High	13 (1.0)	.46 (1.2)	.026(.058)	16 (1.2)	.53 (1.1)	.052(.076)	26 (2.0)	.72 (0.8)	.246(.273)
Integrilin Low	13 (1.0)	.45 (1.2)	.023(.047)	15 (1.2)	.49 (1.1)	.031(.058)	19 (1.5)	.52 (1.3)	.025(.048)
Coronary inter: Placebo	22 (1.7)	Pla vs	Pla vs	24 (1.9)	Pla vs	Pla vs	37 (2.9)	Pla vs	Pla vs
Integrilin High	13 (1.0)	.59 (0.7)	.178(.213)	20 (1.6)	.83 (0.3)	.647(.609)	36 (2.8)	.97 (0.1)	.997(.894)
Integrilin Low	11 (0.8)	.49 (0.9)	.073(.121)	23 (1.8)	.95 (0.1)	.968(.914)	35 (2.7)	.93 (0.2)	.865(.823)

Sponsor's results extracted from Tables E-1 thru E-4; *: reviewer's results (underlined and/or in parentheses) are by STATXACT;
UD=undefined OR (due to zero event rate for Integrilin)

At 30 days there is a trend in the Integrilin low dose group which at 24 and 48 hours appears to be significant. It is surprising that the high dose group, really very little different from the low dose group, is not significant or even trending at 30 days. The picture at 24 and 48 hours is better, but the absence of replication by the two dose groups is troubling.

Since not all randomized patients had angioplasty, an all patients treated analysis was done, and the results are close to significant for the low dose group for the primary endpoint. The medical officer provided the following table comparing ITT and treated patient results.

Table 7-12 Incidence of CEC-Adjudicated Composite Events at 24 Hours and 30 Days in Randomized and Treated Patients

Time Point	High Dose vs Placebo	Low Dose vs Placebo	High Dose vs Placebo	Low Dose vs Placebo
	Randomized Patients		Treated Patients	
24 Hours: Integrilin	7.0% (93/1333)	6.8% (92/1349)	6.9% (89/1286)	6.6% (86/1300)
Placebo	9.3% (124/1328)	9.3% (124/1328)	9.6% (123/1285)	9.6% (123/1285)
%Reduction* (p-value)	24.7% (0.026)	26.9% (0.017)	28.1% (0.014)	31.3% (0.006)
30 Days: Integrilin	9.9 % (132/1333)	9.2% (124/1349)	10.0 % (128/1286)	9.1% (118/1300)
Placebo	11.4% (151/1328)	11.4% (151/1328)	11.6% (149/1285)	11.6% (149/1285)
% Reduction* (p-value)	13.2% (0.219)	19.3% (0.063)	13.8% (0.179)	21.6 %(0.036)

* (Placebo rate minus Integrilin rate) divided by placebo rate
**X^2 tests of Integrilin vs. placebo

The lack of robustness for the 30 day result can be appreciated in that the exclusion of 49 patients from the low dose group and 43 from the placebo group makes a big difference in the outcome. While there is evidence in this study that the drug has activity in this setting, particularly during its administration, this single study is not sufficiently robust to be the sole support for approval. A study is ongoing in unstable angina which may support the case for Integrilin in acute coronary syndromes.

Stephen Fredd, M.D.

cc:
NDA 20-718
HFD-180
HFD-103/Dr. Botstein
HFD-180/Dr. Talarico
HFD-181/CSO/Mr. Folkendt
HFD-180/Dr. Fredd: 3/10/97
f/t deg: 3/10/97/3/11/97wpc:\wpfiles\fredd\m\NDA20718.1sf

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-718 Supplement # ---- Circle one: SE1 SE2 SE3 SE4 SE5 SE6

110 Trade and generic names/dosage form: Integrilin (eptifibatide) Injection Action: (AP) AE NA

Applicant COR Therapeutics Therapeutic Class IIb/IIIa platelet inhibitor

Indication(s) previously approved - NONE -

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication proposed in this application ① treatment of patients with acute coronary syndrome (UA/NQMI) including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). ② treatment of patients undergoing PCI. In this setting, Integrilin has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ __4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See explanation on reverse.

__5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ___No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team Leader (e.g., medical review, medical officer, team leader)

Signature of Preparer and Title

5/13/98
Date

cc: Orig NDA/BLA # 20-718
HFD-110 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-718 Supplement # ------- Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Integrilin (intrifiban) Injection Action: AP TA AE (NA)

Applicant COR Therapeutics Therapeutic Class IIb, IIIa platelet inhibitor

Indication(s) previously approved -NONE-
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application adjunct to Transluminal Coronary Angioplasty (PTCA) for the prevention of acute cardiac ischemic complications related to abrupt closure of the treated coronary vessel.

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__x__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Project Manager — 3/12/97

Signature of Preparer and Title — Date

cc: Orig NDA/~~PLA/PMA~~ # 20-718
HFD-180 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

3/12/97

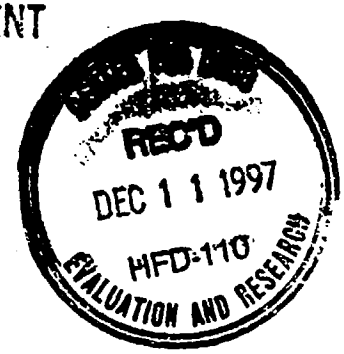
COR THERAPEUTICS, INC.

256 E. Grand Avenue
South San Francisco
California 94080
415 244 6800
Fax 415 244 9208

DUPLICATE

December 9, 1997

NDA ORIG AMENDMENT
(XR)



Division of Cardio Renal Drug Products
Attention: Document Control Room, 10-74
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA Amendment, Section 13, Time Sensitive Patent Information
NDA #20-718
Trade Name: INTEGRILIN™ Injection
Active Ingredient: eptifibatide
Strength: Bolus Injection Vial, 2.0 mg/mL, 10 mL/vial
Continuous Infusion Vial, 0.75 mg/mL, 100 mL/vial
Dosage Form: Injectable Solution

Pursuant to the provisions of 21 C.F.R. §§314.50 and 314.60, we are hereby amending the patent information for the captioned COR Therapeutics, Inc. ("COR") NDA to add the following patent:

U.S. Patent No.:	5,686,570
Expiration Date:	November 11, 2014
Type of Patent:	A compound and pharmaceutical composition patent covering (add generic name of Integrilin here) which is the active ingredient in the INTEGRILIN™ Injection product for which approval is sought.
Patent Owner:	COR Therapeutics, Inc.

DUPLICATE

The undersigned declares (1) that the above-listed U.S. patent covers the INTEGRILIN ™ Injection product, and (2) that the INTEGRILIN ™ Injection product is the subject of the above-listed NDA for which approval is sought under Section 505 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §355.

The Undersigned further declares that a claim of patent infringement under U.S. Patent No. 5,686,570 could reasonably be asserted if a person not licensed by COR, the owner of the above-listed patent, engaged in the manufacture, use, sale of offer for sale of the INTEGRILIN ™ Injection product.

The undersigned declares that this patent information, submitted in duplicate, is being timely filed and is in full compliance with 21 U.S.C. §355(c)(2) and 21 C.F.R. §§314.60 and 314.60.

Sincerely,

Ellen Martin

Ellen Martin
Senior Director
Regulatory Affairs

cc: Zelda McDonald
Division Regulatory Health Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
COR Therapeutics, Inc.	December 9, 1997
TELEPHONE NO. *(Include Area Code)* (650) 244-6872	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 246-7776

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*

256 East Grand Avenue
South San Francisco, CA 94080

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-718

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
eptifibatide	INTEGRILIN™ Injection

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injectable Solution		Intravenous

(PROPOSED) INDICATION(S) FOR USE:

ACA and Unstable Angina

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ■ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CRF 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ■ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Time Sensitive Patent Information

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ■ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

FORM FDA 356h (4/97)

EF

13. PATENT INFORMATION AND CLAIM FOR EXCLUSIVITY

PATENT INFORMATION:

The undersigned declares that the INTEGRILIN™ Injection product is the subject of this application for which approval is sought under Section 505 of the Federal Food, Drug and Cosmetic Act. The undersigned further declares that there are no unexpired U.S. Patent which claims the drug (the active ingredient) in the INTEGRILIN Injection drug product or the INTEGRILIN™ Injection drug product or which claims a method of using the drug or the INTEGRILIN™ drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

CLAIM FOR EXCLUSIVITY:

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (ii) and 505 (j) (4) (D) (ii) of the Food, Drug and Cosmetic Act (FDA) and 21 CFR 314.108 (b) (2), the applicant claims five (5) years of exclusivity for its INTEGRILIN™ Injection Product, which is an intravenously administered dose form.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in CFR 314.108 (a).
3. There are no published studies or publicly available reports of clinical investigations, other than those referenced herein, that are known to the applicant through a computer-assisted literature search that disclose information for the indication for which the applicant is seeking approval for intrifiban.
4. In the opinion of the applicant and to the best of the applicant's knowledge, publicly available information including the scientific literature pertaining to intrifiban does not provide a sufficient basis for the approval of the use of intrifiban administered via this dose form. The applicant's opinion that the studies or reports are insufficient is based on the following:
   - The literature does not contain characterization of the safety or efficacy profiles of intrifiban in this dose form, which are established by the data from the new clinical investigations conducted by the sponsor under IND 35,465 and included in this application.
5. The applicant was the sponsor named in the Form FDA-1571 for IND 35,465 under which the new clinical investigations were conducted.

14. PATENT CERTIFICATION

(Not Applicable)

APPEARS THIS WAY
ON ORIGINAL

13. PATENT INFORMATION AND CLAIM FOR EXCLUSIVITY

PATENT INFORMATION:

The undersigned declares that the INTEGRILIN™ Injection product is the subject of this application for which approval is sought under Section 505 of the Federal Food, Drug and Cosmetic Act. The undersigned further declares that there are no unexpired U.S. Patent which claims the drug (the active ingredient) in the INTEGRILIN Injection drug product or the INTEGRILIN™ Injection drug product or which claims a method of using the drug or the INTEGRILIN™ drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

CLAIM FOR EXCLUSIVITY:

1. Pursuant to the provisions of Sections 505 (c) (3) (D) (ii) and 505 (j) (4) (D) (ii) of the Food, Drug and Cosmetic Act (FDA) and 21 CFR 314.108 (b) (2), the applicant claims five (5) years of exclusivity for its INTEGRILIN™ Injection Product, which is an intravenously administered dose form.
2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in CFR 314.108 (a).
3. There are no published studies or publicly available reports of clinical investigations, other than those referenced herein, that are known to the applicant through a computer-assisted literature search that disclose information for the indication for which the applicant is seeking approval for intrifiban.
4. In the opinion of the applicant and to the best of the applicant's knowledge, publicly available information including the scientific literature pertaining to intrifiban does not provide a sufficient basis for the approval of the use of intrifiban administered via this dose form. The applicant's opinion that the studies or reports are insufficient is based on the following:
   - The literature does not contain characterization of the safety or efficacy profiles of intrifiban in this dose form, which are established by the data from the new clinical investigations conducted by the sponsor under IND 35,465 and included in this application.
5. The applicant was the sponsor named in the Form FDA-1571 for IND 35,465 under which the new clinical investigations were conducted.

EXCLUSIVITY SUMMARY for NDA # 20-718 SUPPL #_____

Trade Name Integrilin Generic Name eptifibatide

Applicant Name COR Therapeutics HFD- 110

Approval Date, if known 5/18/98

PART I **IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /✓/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical

investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /___/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

   _____

   _____

   YES /___/ NO /___/

   (b) Did the applicant submit a list of published studies

relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ 3/4/98

Signature Date

Title: Regulatory Health Project Manager

_____ 3/4/98

Signature of Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

COR THERAPEUTICS, INC.

256 E. Grand Avenue
South San Francisco
California 94080
415 244 6800
Fax 415 244 9208

See Page 4

April 1, 1996

Stephen Fredd, MD
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Attention: Document Control Room 10-74
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20851

Subject: **INTEGRILIN™ (intrifiban) Injection**
Intravenous Injection
Original New Drug Application (#20-718)
User Fee ID #2976

Dear Dr. Fredd:

Submitted herewith is a New Drug Application (NDA) #20-718 for INTEGRILIN™ (intrifiban Injection), a prescription drug which is intended as an adjunct with aspirin and heparin in the treatment of patients undergoing coronary angioplasty for the prevention of acute coronary complications related to abrupt closure of the treated coronary vessel.

Integrilin™ Injection is supplied in the following configurations, 1) a bolus injection vial (2.0 mg/mL, 10 mL) and 2) an infusion vial (0.75 mg/mL, 100 mL).

Please note the following information relevant to the specified sections of this original New Drug Application:

Section 3. - Chemistry, Manufacturing and Controls:

- As requested by the Division at the December 20, 1995 Pre-NDA CMC meeting, an additional copy of volumes 1.2 through 1.13 have been provided for the Microbiology Reviewer.

- In accordance with 3.14.50(d)(1)(v), we certify that a field copy of the Chemistry, Manufacturing and Controls Section of this application has been sent to the Applicant's home FDA District Office in San Francisco, California.

- An Environmental Assessment was completed in accordance with Format 1 (21 CFR §25.31a) and the Guidance to Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. In accordance with the guidance document, Integrilin has qualified for the "Tier 0" approach for fates and effects testing.

Section 4. - Samples, Methods Validation and Labeling:

The three additional copies of the "Methods Validation Package" are being retained by COR Therapeutics, Inc. with the product samples until notification from the Division to submit.

Section 7. - Microbiology:

This section is not applicable for this NDA.

Section 8. - Clinical Data:

- All clinical study reports are numbered from page 1 of the report to the end of that report including appendices and references with the exception of Study Report 93-014 which is paginated 1 through to the end of each volume. For the remainder of the NDA, summaries as well as reports and references are paginated and are clearly marked by a tab within its particular volume.

- The pharmacokinetic ASCII data sets for the Phase III clinical study, 93-014, are provided for the Biopharmaceutics reviewer on diskettes which are located in a copy of the Application Summary (Volume 1.1) provided with the review copy of Section 6., Pharmacokinetics and Bioavailability.

Section 9. -Safety Update:

This information will be provided four months from receipt by FDA of this application.

Section 10. - Statistical:

This section is identical to corresponding portions of Section 8.

Section 11. - Case Report Form Tabulations:

As agreed to at the Pre-NDA meeting held between COR Therapeutics, Inc. and the Division on November 9, 1995, case report form tabulations for clinical studies 92-009 and 93-014 will be viewed and printed from the Computer-Assisted New Drug Application (CANDA) and will not be provided in the NDA; case report form tabulations are provided for all other studies in the NDA. The Division agreed on March 26, 1996 that the CANDA need not be delivered until approximately 2 to 3 weeks from the date of the NDA submission and that, therefore, the absence of the case report form tabulations for clinical studies 92-009 and 93-014 in the NDA submission would not prompt a refusal to file.

Section 12. - Case Report Forms:

Case report forms have been provided for deaths and discontinuations due to adverse events for all clinical studies. All case report forms for clinical studies 92-009 and 93-014 can be viewed and printed from the CANDA.

Section 13. - Patent Information and Claim of Exclusivity:

This information is located directly behind this cover letter.

Section 14. - Patent Certification:

This section is not applicable to this NDA.

Section 15. - Other:

This section includes a summary of agreements reached between COR Therapeutics, Inc. and the Division having direct bearing on the information contained within this application and is located directly behind this cover letter.

General:

- The generic name "intrifiban" has been submitted to the USAN Council for a USAN name designation. However, as of the date of this submission, this designation is still pending.

- The following names for Integrilin™ that appear in this NDA are synonymous: C68-22, Integrelin, Integrilin, and SCH 60936.

- In accordance with the provisions of Sections 505 (c)(3)(D)(iii) and 505(j)(4)(D)(ii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR 314.108(b)(4), exclusivity is claimed for this product. Information in support of the claim for exclusivity is provided in section 13 of this application. However, as stated previously, the patent for Integrilin™ is still pending.

- In accordance with Section 306(k) of the Food, Drug and Cosmetic Act, COR Therapeutics, Inc. certifies that, with respect to this application, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

•

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331 (j).

The Applicant contacts include the following:

For questions concerning the NDA:
Ellen L. Martin
Director, Regulatory Affairs
(415) 244-6872

For questions concerning the CANDA:
Robert Sturm
Biometric Research Institute, Inc.
(415) 244-0355

Sincerely,

Ellen L. Martin
Director, Regulatory Affairs

Attachment

cc: Julie DuBeau, CSO (cover letter only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : MAR 10 1998

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval (Approvable) of NDA 20-718, eptifibatide (Integrilin), COR Therapeutics, Inc.

TO : Director, Office of Drug Evaluation I, HFD-101

Introduction

This transmittal memorandum also is intended to serve as the secondary review of NDA 20-718. The Division and the Cardiac and Renal Drugs Advisory Committee (which met on January 28, 1998) recommend that eptifibatide be approved. There is no question about that. The patient population that should be treated and the dose to use are matters of clinical judgement. I will try to lay out the considerations in what follows. It is appropriate to read the Summary of Summaries before going further.

My judgement is that eptifibatide should be approved "as an adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PTCA) for the prevention of acute cardiac ischemic complications, including death, myocardial infarction or re-infarction, in patients at high risk for abrupt closure of the to-be-treated coronary vessel," and the dose to use should be a 180 microgram/kg bolus, followed by an infusion of 1.3 micrograms/kg/min for 20 to 24 hours.

The Advisory Committee recommended that eptifibatide should be approved "as an adjunct to percutaneous transluminal coronary angioplasty or atherectomy (PTCA)," and the dose to use should be a 135 microgram/kg bolus, followed by an infusion of 0.5 micrograms/kg/min for 20 to 24 hours.

Major Clinical Trials

All told there were 20 completed clinical trials at the time of the January, 1998 Advisory Committee meeting. Eight of these were conducted in normal volunteers (involving 133 subjects), 6 were Phase II studies oriented toward dose selection (involving 669 patients), 4 were small exploratory studies oriented toward other indications (involving 235 patients or subjects). The 2 major trials involved a total of 14,958 randomized patients and have been the major focus, and the results of 2 other trials PERIGEE and PRIDE were also reviewed . Results of the other 16 studies were examined or referred to, when appropriate, but there has been no exhaustive review of them by this Division. The original submission (IMPACT II and ancillary trials) having been reviewed by the Division of Gastrointestinal and Blood Coagulation Products.

IMPACT II
This was a double-blind, parallel group (3 groups, placebo, eptifibatide 135 ug/kg bolus/0.5 ug/kg/min infusion, eptifibatide 135 ug/kg bolus/ 0.75 ug/kg/min infusion) trial that randomized 4010 patients (no age limit specified in the protocol) who were scheduled to undergo coronary angioplasty (a variety of procedures, both elective and "emergency") at 82 medical centers. Most patients received aspirin (protocol specified as 325 mg) within 24 hours of angioplasty and intravenous heparin (targeting ACT between 300-350 seconds and aPTT of 2 to 3 times baseline). Other therapies were at the discretion of the investigator. Within the study was another study that evaluated a "stent kit."

The primary endpoint was a **combination** of **(1) all cause mortality, (2) myocardial infarction and (3) need for urgent intervention.** All endpoints were adjudicated by a blinded, independent Clinical Events Committee (CEC). The number of events that had accumulated up to **30-days** was the pre-declared primary efficacy evaluation. According to the protocol, the primary analysis was to be an intent-to-treat, **or** "treated as randomized" pairwise comparison between the 3 treatment groups using chi-square methods.

PURSUIT

This was a double-blind, parallel group (3 groups, placebo, eptifibatide 180 ug/kg bolus/1.3 ug/kg/min infusion, eptifibatide 180 ug/kg bolus/2.0 ug/kg/min infusion) trial that randomized 10,948 patients from 726 centers and 27 countries. Patients randomized were mainly 75 years of age or younger, and had "unstable angina" characterized as 1) symptoms of cardiac ischemia at rest lasting at least 10 minutes within 24 hours of enrollment, 2) any of a variety of ST-T wave abnormalities, OR subsequent positive CK-MB. Most patients received concomitant aspirin (38 to 1500 mg) and could receive intravenous heparin with a target aPTT of 50 to 70 seconds. The 180 bolus/1.3 infusion arm was discontinued as the trial progressed which resulted in 4739 patients randomized to placebo, 1487 patients randomized to the 180/1.3 dose, and 4722 patients randomized to the 180/2.0 dose.

The primary endpoint, differing from that of IMPACT II, was a **combination** of **(1) all cause mortality, and (2) myocardial infarction.** All endpoints were adjudicated by a blinded, independent CEC. The number of events that had accumulated up to **30-days** was the pre-declared primary efficacy evaluation. According to the protocol, the primary analysis was to be pairwise comparison between 2 treatment groups using chi-square methods. It was planned that one arm of the study would be dropped.

Platelet Inhibition Background

Eptifibatide is a GP IIB/IIIa blocker that has a rapid onset of action (i.e., immediately, following an intravenous bolus) and is readily reversible upon discontinuation of the drug (approaching baseline in 4 hours). Its major known effect is to inhibit platelet aggregation.

As outlined in the following table, there have been 4 dosing regimens of eptifibatide studied in the two major trials.

Trial Name	Bolus Dose	Infusion Rate	Duration of Infusion
IMPACT II	135 ug/kg	0.50 ug/kg/min	20 to 24 hours
IMPACT II	135 ug/kg	0.75 ug/kg/min	20 to 24 hours
PURSUIT	180 ug/kg	1.30 ug/kg/min	72 hours
PURSUIT	180 ug/kg	2.00 ug/kg/min	72 hours

Eptifibatide is administered intravenously. It has a terminal elimination half-life of about 2 to 3 hours. When administered as a constant-rate continuous infusion, it reaches steady-state plasma concentration in about 6 to 8 hours. Steady-state plasma concentrations following a constant-rate continuous infusion of 0.5 micrograms/kg/min are somewhat greater than 200 ng/ml, and after infusion, 2.0 micrograms/kg/min plasma concentrations are about 1000 ng/ml. The pharmacokinetics are reasonably orderly and linear. In order to achieve desired plasma concentrations quickly (in minutes), the 2 to 3-hour half-life requires a dosing regimen that involves a "loading" bolus dose followed by an infusion.

The IMPACT II dosing regimens can be taken as having achieved between 30 to 60 % inhibition of in-vitro ADP-induced platelet aggregation and the PURSUIT dosing regimens as having achieved 80 to 90+ % inhibition of in-vitro ADP-induced platelet aggregation (when blood for measurement is PPACK collected), at steady-state. I think it is reasonable to say that the platelet aggregation inhibition is best described by a near linear relationship to the logarithm of the eptifibatide plasma concentration.

It is important to note, however, that there is a monotonic time course to the platelet aggregation effect because the bolus/infusion dosing regimen is not really a square wave for eptifibatide plasma concentration (see Dr. Gordon's review of the PERIGEE study, particularly Figure 2 of her review). The % of patients achieving at least 80% platelet aggregation inhibition were 83%, 48%, 54%. 84%, 100% and 100% at 5 min., 1 hour, 4 hours, 24 hours, 48 hours, and 72 hours, respectively. Note that at 1 hour less than half of the patients had at least 80% inhibition. The dosing regimen that gave these results was the 180 microgram/kg bolus, followed by an infusion of 2.0 micrograms/ kg. This was also true, but to a somewhat lesser extent in the PRIDE study.

Results of the 2 Major Trials

What follows is considerably abbreviated. For example, the PURSUIT study protocol and its amendments total 119 pages of single spaced, one-side of the page typing. Medical reviews written by Dr. Isaac Hammond (PURSUIT), Dr. Lilia Talarico (IMPACT II), Dr. Maryann Gordon (PERIGEE), and Dr. Douglas Throckmorton (PRIDE), as well as statistical reviews written by Dr. Nuri (PURSUIT) and Dr. Sankoh (IMPACT II) are in the attachments to this transmittal memorandum, as are reviews by Dr. Ali Al-Hakim (Manufacturing and controls), Dr. Paul Stinavage (Microbiology), Drs. Hae-Ryun Choi and Ameeta Parekh (Biopharmaceutics), Dr. Indra Antionipillai (pharmacology) and a Division Director's transmittal memo written by Dr. Fredd on March 10, 1997.

Also attached is the briefing document prepared by Cor for the January 28, 1998 Advisory Committee meeting as well as a copy of their slides. I think you can read anywhere you wish and/or take data from anywhere you wish. There are no substantive disagreements with respect to data, nor p values. To make numbers add up, it is important to track whether the analysis described is intent-to-treat (all patients randomized) or treated-as-randomized.

IMPACT II

Although the selection of doses to study could be questioned (it is still not clear what doses might have been worthy of study), the study was well planned, well executed, passed routine field inspections, and cannot be faulted in any major way. It is noteworthy that in addition to the CEC adjudicated events (which were the declared primary endpoint), investigators were asked to record their interpretation of clinical outcome and those results were also analyzed. The protocol did not specify whether an intent-to-treat or a treated-as-randomized analysis would be the analysis of principal interest, but a submission from COR dated June 2, 1995 (prior to any unblinded analysis) said the analyses would be done both ways.

The **event** analyzed was the combined end-point (**death, myocardial infarction, urgent intervention**). The principal statistical test (prespecified and used by the sponsor) was the Chi square statistic.

The intent-to-treat results of IMPACT II (page 60 of Dr. Talarico's review) are shown in the following table. Since the intended analysis was to do a pairwise comparison and declare a winner if either eptifibatide group was superior to placebo, to preserve a nominal p of 0.05, the comparison would have had to have a **p of 0.035** or less (a number **predeclared** by COR). Nobody really disagrees with this. Note the p was about twice as large as needed.

Treatment Group	Number Randomized	Events	FDA 2-Sided p	Sponsor 2-Sided p
Placebo	1,328	151		
eptifibatide Low Dose		124	Not Done	0.063
eptifibatide High Dose		132	Not Done	0.219
Total	4,010	407		

According to this table 11.4 % (151/1,328) of patients in the placebo group had an event and 9.5 % of patients in both eptifibatide groups (256/2,682) had an event. This corresponds to a 2 % reduction of events in the eptifibatide groups, compared to placebo ($0.025 < p < 0.05$, nominal, my calculation).

A treated-as-randomized analysis was performed because not all randomized patients received study drug, for a variety of reasons. The sponsor argues that it is entirely reasonable to analyze the data according to whether or not the patient actually received study drug or actually got PTCA. Note that both the number of events and the number of patients at risk changes. Dr. Sankoh, in the FDA analysis, elected to use exact statistical methods (STATEXACT), not the Chi square statistic.

Treatment Group	Number Got Treated	Events	FDA 2-Sided p	Sponsor 2-Sided p
Placebo	1,285	149		
eptifibatide Low Dose		118	0.041	0.035
eptifibatide High Dose		128	0.201	0.179
Total	3,871	395		

The "low dose" treatment effect being 31 events prevented (2.384% or 2,384 events prevented per 100,000 patients treated). That for the "high dose" being 1,633/100,000.

Investigators also recorded study endpoints, and an analysis was conducted (treated-as-randomized) by the sponsor. Of note is that investigators recorded fewer total events than did the CEC, a finding that will be repeated in PURSUIT.

Treatment Group	Number Randomized	Events	My Chi square	Sponsor 2-Sided p
Placebo	1,285	97		
eptifibatide Low Dose		70	0.025<p<0.05	0.025
eptifibatide High Dose		80	0.1<p<0.2	not found
Total	3,871	247		

The time-course of treatment effect (if any) might be gleaned from the following table based upon a treated-as-randomized analysis that was conducted by the sponsor

Post-Randomization Time Period Ending	Placebo Events (n = 1,285)	eptifibatide Low Dose Events (n=1,300)	eptifibatide High Dose Events (n=1,286)
"Abrupt Closure"	65	36	43
		p=0.003	p=0.030
24 Hours	123	86	89
		p=0.006	p=0.014
48 hours	131	99	102
		p=0.021	0.045
30 Days	149	118	128
		p=0.035	p=0.179

The "abrupt closure" is post-hoc (not really, talked about in meetings but not in the protocol), but impressive. The high-dose group, as is true for all other analyses, fared less well than the low-dose group.

Summary of IMPACT II efficacy analyses. Various analyses abound throughout the documentation created by the sponsor and by FDA, many of them of interest but not summarized here. Among the issues examined was the relative contribution of death and myocardial infarction (irreversible outcomes) as opposing to non-irreversible "urgent intervention." Irreversible outcomes contributed 80% of all events, but the incidence of death (a total of 31) or myocardial infarction (a total of 282) at 30 days did not show a statistically significant ($p > 0.05$) difference between groups, on their own nor when combined.

Although, IMPACT II "seems" to have found something which was internally consistent and sensible (e.g., affecting short term ischemic processes more than long-term ischemic processes and not having the short-term effects wash away with longer follow-up), the Division, the Advisory Committee, the Division of Gastrointestinal and Coagulation Drug Products and ODE III each concluded in February/March 1997 and the Division and the Advisory Committee again in January 1998 concluded that this single trial was not convincing enough to gain a "single trial" approval for eptifibatide for any indication (even without considering adverse effects).

PURSUIT

Out of the 10,948 patients randomized, only 22 were "lost to follow-up." At this instant I have forgotten the number, but at the time of the Advisory Committee meeting, greater than 10 of the 22 had been found and their outcome determined. None of those found had had an event. So, for practical purposes, there can be more than reasonable confidence that "lost to follow up" cannot be a confounder and/or weaken inferences that might be taken from the study.

All analyses were conducted as intent-to-treat, unless specified differently. **Events** are the combination of **1) all cause mortality or 2) documented myocardial infarction.** There were a total of 1,417 events observed within 30 days (180 deaths, 1,075 myocardial infarctions, and 162 patients both died and had a myocardial infarction). So, events were plentiful, and all were of irreversible quality.

The study was conducted world-wide. Results (expressed as odds ratios) from North America (United States, and Canada) as well as those of the study as a whole favored eptifibatide and the 95% confidence limits (for odds ratio, intent-to-treat) did not overlap 1.0. For all other regions (Western Europe, Eastern Europe and Latin America) the 95% confidence limits overlapped 1.0 and for Latin America and Eastern Europe the point estimates favored placebo for events adjudicated by the Clinical Events Committee but not for those judged by investigators alone. Although interesting, the Advisory Committee and I think that not much time should be devoted to speculation about this finding and that the study as a whole, using the CEC adjudicated events, is what should be paid attention to.

Overall result. The principal result, intent-to-treat, all cause mortality and/or myocardial infarction (the prespecified primary endpoint, CEC adjudicated events) analyzed by Chi square methods, is shown in the following table.

Placebo	Eptifibatide 180/2.0		p required to
n = 4,739	n=4,722	p	preserve p = 0.05
745 (15.7%)	672 (14.2%)	0.042	0.0478

The treatment difference being 73 events (1.55%, or 1,550 events prevented per 100,000 patients treated). The dose used was the **180 microgram/kg bolus followed by an infusion of 2.0 micrograms/kg/minute** for 72 hours.

For investigator noted events the results for the **180 microgram/kg bolus, 2.0 micrograms/kg/minute** infusion were as follows, a retrospective analysis.

Placebo	Eptifibatide 180/2.0	
n = 4,739	n=4,722	nominal p
475 (10.0%)	380 (8.1%)	0.001

The treatment difference being 95 events (2.01% or 2,010 events prevented per 100,000 patients treated).

For the discontinued arm of the study, namely the **180 microgram/kg bolus followed by an infusion of 1.3 micrograms/kg/minute** for 72 hours, the results were as follows.

Placebo	Eptifibatide 180/1.3	
n = 4,739	n=1,487	nominal p
745 (15.7%)	200 (13.45%)	0.01<p<0.05

This treatment difference is about 34 events (assuming both groups had 1,487 patients), a difference of about 2.25% (or **2,250 events prevented per 100,000 patients treated**). This is clearly a retrospective analysis. It is a larger treatment effect than was present for the higher dose, see above, and was more "statistically" significant than that of the primary analysis. I guess it was "too safe" to continue the arm.

All cause mortality in the eptifibatide group, although in the right direction was on its own not differentiable from that of the placebo group (p=0.531) and myocardial infarction or reinfarction (adjudicated by the CEC) was similarly in the right direction but the eptifibatide group was not differentiable from the placebo group (p=0.137), but by investigators' assessment it was (p = 0.002).

It is worth noting that Dr. Nuri in his review (page 4 of his review) lists 4 methods appropriate to apply to the data. On a whole, each come out saying the same thing, and he further concludes that the exact p-value for the ITT analysis (odds ratio) is 0.0454. Anyway one cuts this cake, a p just a hair below 0.05 was found by PURSUIT for its primary endpoint. So, conventional statistical significance was achieved by about 0.0050 p units, a pretty narrow margin, for the primary endpoint.

Indeed, careful consideration was given at the Advisory Committee to consideration of penalties for interim looks, not including the low dose eptifibatide arm in analyses, Chi square and other statistics, etc. The discussion which involved Drs. Fleming, Fisher, Kerry Lee, Sankoh, and the Advisory Committee including Dr. Moye' occupied 30 to 45 minutes and will not be repeated here. The above tables can be taken as written, without question about whether some other number would be more appropriate, less conservative, more conservative, etc. There are no legitimate statistical concerns to discuss. Each of the other tables and p values that follow are similarly "squeaky clean." It is important, at this juncture, to note that in places that follow, the p values start to approach 0.00125 (but the "best" still miss by about an order of magnitude). Of course, where they do, they represent subgroup analyses, sometimes non-prespecified analyses and should not be taken as representing the trial as a whole. The trial as a whole had about 1 chance in 20 of giving a incorrect inference that eptifibatide was favored over placebo.

The time-course of treatment effect (if any) might be gleaned from the following table based upon an all randomized analysis (ITT) that was conducted by the sponsor.

Time After After Randomization	Placebo n = 4,739	Eptifibatide n = 4,722	p
96 Hours	429(9.1%)	359(7.6%)	0.011
7 days	552(11.7%)	477(10.1%)	0.016
30 days	745(15.7%	672(14.2%)	0.042

A post-hoc look at the course of patients randomized.

A Problem?

This was an "all comers," or "real life" trial. All patients who qualified as "unstable angina," or "acute coronary syndrome," or "non-Q-wave myocardial infarction" were enrolled throughout the world. All patients were treated according to the physicians best judgement, with the exception of patients being randomized to placebo or to eptifibatide. Pretty much for sure (somewhere in the range of 1 in 20 chances of being wrong) there was a treatment effect detected that favored eptifibatide.

There was a wide difference with respect to "standard patient care" throughout the world, as reflected in the results of the trial. In North America, by 30 days 82% of patients had had a diagnostic coronary angiogram, 35% had had some form of percutaneous coronary artery intervention (PTCA, stent, etc.), and 21% had had CABG. In Eastern Europe, the figures were 25%, 7.4% and 7.0% for angiography, coronary intervention and CABG, respectively. More than half, according to COR, of these procedures occurred between 96 hours and 30 days after randomization, on the "late" side. There were no statistically significant differences found with respect to either the incidence of any of these 3 interventions nor with respect to the outcomes of the interventions (although every point estimate, either incidence of the intervention or outcome of the intervention, favored eptifibatide). One could take comfort in that, the treatment effect was detectable despite a wide heterogeneity of standard clinical care.

On the other hand, I worry some. Treat anybody with "unstable angina," simply because a trial was conducted and the result came in a whisker below a p of 0.05 (but is intuitively appealing and has non prespecified analyses that look very strong)? Add another therapy on top of heparin and aspirin (neither of which we know much about) on the basis of a single trial whose results came in a whisker below a p of 0.05 (but is intuitively appealing and has non prespecified analyses that look very strong)? I am pretty sure, but not absolutely sure, that had the PURSUIT p been 0.075 we would not be considering approval. Yet, a p of 0.075 is not much worse than a p of 0.05 and I know for sure that I am willing to accept the high dose IMPACT II trial as being consistent with having shown a treatment effect (and it had a p of 0.219, ITT). The marginality of p values is not the problem, once the 2 trials are put together.

So I would like to know who got the treatment benefit, although I know that the trial was not designed to answer that question. In fact, the complexity of the trial defies getting a precise answer, but what follows is an attempt to understand what the trial found.

Using Percutaneous Intervention Within 72 Hours As An Arbitrary Time Marker

Because the sponsor had chosen this marker and had presented a description of events utilizing this marker, I think it is worth the effort to try to describe these results and try to understand the treatment effect found. It turns out to not be a straightforward descriptive problem. The diagram, below, describes the overall flow of patients from the time of randomization, organized by whether of not percutaneous intervention occurred within the first 72 hours after randomization. The "events" are those recorded by 30 days for the selected population.

As depicted in the diagram, ((619 + 631)/(4722 + 4739) X 100) = 13.2 % of randomized patients had percutaneous intervention by 72 hours. This represents a somewhat small sample of all interventions (e.g., the diagram does not indicate who did or who did not have CABG) that occurred during the trial. By 30 days, among the randomized patients, there had been 5,982 coronary procedures done which included CABG, PTCA, and stent placement, so the diagram represents only about 21% of the major procedures done during the entire course of the trial.