CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-873

MEDICAL REVIEW

FEB - 8 2000

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	NDA 20-873 (BZ); (BM)
Sponsor:	The Medicines Company
Drug name:	Angiomax (bivalirudin) Injection
Date submitted:	November 11, 1999; December 20, 1999; January 7, 2000
Date Received:	November 12, 1999; December 21, 1999;
Review completed:	February 3, 2000
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
The sponsor is seeking approval of Angiomax (bivalirudin; Hirulog), a direct thrombin inhibitor, for use as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). This is the third review cycle for this application. A summary of the regulatory history for this NDA is as follows:

Cycle 1: The NDA was originally submitted December 23, 1997. A non-approval letter was sent on November 18, 1998 citing failure to demonstrate a benefit of bivalirudin over the comparator (heparin) for the primary efficacy endpoint (procedural failure) in the two pivotal clinical efficacy trials and Chemistry, Manufacturing, and Controls deficiencies. (Please see my Medical Officer's Review dated 10/6/98). The sponsor was advised to consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of bivalirudin, compared to heparin, in post-MI patients undergoing PTCA for the treatment of unstable angina.

Cycle 2: The sponsor responded to the non-approval letter on 3/3/99 with a submission that included additional analyses of data from the previously submitted efficacy studies, a summary discussion of clinical effects of bivalirudin [including an estimation of the clinical effects of bivalirudin and heparin in PTCA compared to an "imputed placebo" based on three literature reports], and a review of evidence supporting the view that bivalirudin is associated with less hemorrhage than heparin in PTCA patients. (See Medical Officer's Review dated 10/6/99). An approvable letter was sent on 10/28/99 for the application identifying a number of Clinical, CMC, and Biopharmaceutical deficiencies. The letter stated regarding the sponsor's response that: "Although these pieces of evidence collectively assist in bringing the Agency closer to a determination that Angiomax™ is safe and effective for use as an anticoagulant in patients with unstable angina undergoing PTCA, these data do not provide substantial evidence of effectiveness consisting of adequate and well-controlled clinical trials." The letter stated that an additional clinical trial is needed. The needed trial was described as a prospective, adequate- and well-controlled clinical trial of the effects of Angiomax compared to heparin, as conventionally

used and monitored. Either a superiority trial or non-inferiority/equivalence trial would be acceptable. CMC deficiencies and Biopharmaceutics deficiencies also were cited.

Cycle 3: The sponsor responded to the approvable letter on 11/11/99. This submission consists of 4 volumes containing a cover letter, summary of previous meeting and discussions between sponsor and FDA, draft labeling, response to CMC issues, response to Biopharmaceutics issues, response to Clinical/Statistical issues and Safety Update. The submission does not contain any new data or analyses not previously submitted to the Agency. The indication being sought has been changed to: "Bivalirudin is indicated as an anticoagulant for patients undergoing percutaneous coronary angioplasty for unstable angina presenting within two weeks of myocardial infarction." The sponsor does not propose any new efficacy study. A Clinical Safety update covering the period up to October 31, 1999 is included. [Because there has been a further increase of only 7% (175 patients) in number of PTCA patients exposed to bivalirudin, no new overall safety analysis has been conducted]. Additional safety information was submitted 12/20/99 in the form of Data Safety Monitoring Board (DSMB) Report for HERO-2 Protocol.

After cursory review of the resubmission, the Division held a teleconference with the sponsor on December 13, 1999 to give direction to the firm regarding the remaining clinical/statistical issues to help provide a framework for discussion at the planned meeting with the sponsor scheduled for 1/25/00 regarding this application.

During the teleconference the sponsor was asked to address four issues:

1. inadequacy of the heparin regimen used as comparator in the two pivotal studies (the regimen may have contributed to the bleeding advantage seen for bivalirudin);

2. accountability of heparin usage in patients after discontinuation of bivalirudin;

3. rationale for bivalirudin's apparent effectiveness in a sicker post-MI subgroup but not in the overall population studied; and

4. the sponsor's proposed misleading labeling which addresses results for only the post-MI subgroup in the Clinical Trials sections.

On January 7, 2000 the sponsor provided a background package for the 1/23/00 meeting. For this review I have examined information in the sponsor's 11/11/99 response to the approvable letter, the 12/20/99 DSMB report, and the material provided in the meeting background package.

Summary of Information Provided:
11/11/99 Resubmission: The sponsor provides a discussion of support for use of bivalirudin for PTCA in post-MI patients. This information in this submission is summarized briefly below with reviewer's comments.

1. The sponsor proposes that pooling studies C-92-304-1 and C92-304-2 is permissible because the two studies used the same protocol and that integrated analysis of the two trials was planned prospectively.
   Reviewer's comment: The two studies did use the same protocol so pooling the studies is not unreasonable. However, even if the studies are pooled, some

standard of internal consistency/consistency between the two studies should be met. The 3/12/93 letter the sponsor cites as indicating that an "integrated analysis" of the two studies would be done actually was written in response to a 2/23/93 letter from the Division in response to the sponsor's original plan to analyze C92-304-P as a single study. The Division's letter urged the sponsor to "conduct a large phase 3 trial that is designed to be analyzed as two separate studies or conduct two separate phase 3 studies as you had originally planned." The sponsor's 3/12/93 letter indicates that two studies would be done and states: "At both the interim and final analysis, each of the two studies will be analyzed separately and a combined analysis will be performed on all patients enrolled in both studies."

2. The sponsor proposes that extracting the post-MI patient population from C-92-304-1 and C-92-304-2 as a subpopulation for purposes of efficacy analysis is permissible because patients entering the two studies were prospectively stratified on the basis of whether they were classified as Braunwald Class B (primary unstable angina) or Braunwald Class C (post-MI unstable angina). This stratification was done because an earlier registry trial showed a higher rate of procedural failure (death, MI, revascularization or abrupt vessel closure) in the post-MI patients.
Reviewer's comment: The post-MI population constituted 19% of randomized patients in C-92-304-1 and 15% of randomized patients in C-92-304-2. A significant efficacy result for the primary endpoint (procedure failure) in the post-MI population was seen only in Study C92-304-2 and this study drives the results in the combined analyses of C92-304-1/2, even though C92-304-1 had more post-MI patients than did C-92-304-2, (409 and 332 patients, respectively). The efficacy result of the analysis of the post-MI population data should be confirmed in a prospectively planned study.

3. The sponsor proposes that the strong benefit on "major hemorrhage" seen in both studies constitutes a clinically important benefit.
Reviewer's comment: In both studies the bivalirudin group clearly showed less major hemorrhage as compared to the heparin group. However, the heparin regimen used was somewhat more aggressive than is customarily used for PTCA and the degree of anticoagulation with heparin was not monitored after target ACT had been achieved. Both of these factors may have led to more bleeding in the heparin patients.

4. The sponsor proposes that the effectiveness of bivalirudin in PTCA is substantiated by "other related studies" including C92-301 (TIMI-7), C93-309 (TIMI-8), and C90-041 (Topol).
Reviewer's comment: Applicability of these studies to the use of bivalirudin in PTCA is discussed in my Medical Officer's Review dated 10/6/99 (pages 3-6). TIMI-7 was a dose response study of bivalirudin in 410 patients with unstable angina. Study C90-041 was a dose-ranging study of bivalirudin in 291 patients undergoing PTCA in which many patients had bivalirudin dose adjusted during the study and only 12 patients received the bivalirudin dose ultimately used in C92-304. Study C93-309 (TIMI-8) was a study of bivalirudin versus heparin in acute coronary syndromes (unstable angina or non-Q-wave MI) planned for 5320 patients that was terminated for "business reasons" after enrollment of 133 patients. (See page 8 of my Medical Officer's Review dated 10/6/98).

5. The sponsor proposes that the effectiveness of bivalirudin in PTCA is substantiated by superiority over imputed placebo in the overall trial population and in the post-MI population.
Reviewer's comment: The sponsor's case for the imputed placebo is presented and discussed in my Medical Officer's Review dated 10/6/99 (pages 6-16) and in the FDA Statistical Review dated 10/13/99. Basically, the sponsor's argument rests on accepting ACT as a surrogate for effective anticoagulation because of observed correlation between adequate ACT and satisfactory outcome of PTCA with heparin anticoagulation, though this has not been tested in a prospective study to establish a cause-and-effect relationship. Because there is no standardized heparin regimen for use in PTCA, it is even more difficult to estimate an effect size for heparin in PTCA using the available information.

6. The sponsor requests a full waiver of the pediatric assessment requirement based on the indication sought, in that the drug product is unlikely to be used in a substantial number of pediatric patients for this indication.
Reviewer's comment: The sponsor's request for waiver of the pediatric assessment requirement is reasonable as this indication is almost exclusively applicable to only the adult population.

7. A safety update covering the post-NDA period up to October 31, 1999 is included. An additional 175 patients have been exposed to bivalirudin in 5 PTCA studies, an additional 1615 patients in a study (HERO-2) of anticoagulation plus thrombolysis [redacted] in acute MI, and an additional 8 patients in a study of heparin associated thrombocytopenia (HAT/HITTS). These studies have been described and some safety information presented previously in the Safety Update submitted 8/5/99 covering the period up to May 28, 1999 and reviewed in my Medical Officer's Review dated 10/6/99. Enrollment of patients in the 5 PTCA studies is summarized below.

Table 2. PTCA Studies - Post NDA Submission

Study	Bivalirudin Arm	Comparator Arm	Bivalirudin Patients (planned/completed)	ComparatorPatients (planned/completed)	Study Status
CACHET Pilot Phase A	Biv / ReoPro	Heparin/ReoPro	30/30	30/30	Completed
CACHET Pilot Phase B	Biv/ provisional ReoPro	Heparin/ReoPro	97/85	43/44	Completed
LMWH	Bivalirudin	Heparin	20/20	20/20	Completed
Ticlid Interaction	Biv / Ticlid	Heparin/ Ticlid	15/14	15/15	Completed
[redacted]					
TOTAL			192/175	108/108	

The only new safety information mentioned for these studies is the following: In the CACHET Pilot Study B 2 (4.5%) of the ReoPro/heparin patients experienced an MI as compared to 3 (3.5%) of the bivalirudin patients. Also, 3 bivalirudin patients (3.5%) had major bleeding as compared to 3 (6.8%) of ReoPro/heparin patients and one patient treated with ReoPro required urgent revascularization. Safety information for the HERO-2 study is discussed with the December 20, 1999 submission below. There is no new information for the HAT/HITTS study.

The sponsor states that 148 patients have been treated with an elective stent at the same time as bivalirudin anticoagulation. The sponsor states that there is no indication that bivalirudin use complicates the stent deployment procedure. No data specifically supporting this statement is included in the submission.

Bivalirudin has been approved for marketing in New Zealand (October, 1999). Applications for marketing approval are currently under review in Canada and the European Union.

8. Draft labeling for the product is included in which the indication has been modified to state: "Angiomax is indicated for use an an anticoagulant in patients with unstable angina undergoing percutaneous coronary angioplasty (PTCA) [redacted]

Reviewer's comment: Important modifications to the labeling that were suggested by the Agency in the approvable letter that have not been made in the Clinical Studies section of the new draft labeling submitted are:

[redacted]

[redacted]

January 7, 2000 Briefing Document for 1/25/00 meeting:
This briefing document repeats a lot of the information and discussion contained in the 3/3/99 and 11/11/99 resubmissions. There is additional discussion of the use of ancillary open-label heparin in Studies C92-304-1/2. The sponsor states, "Since the bivalirudin trials were randomized, and the heparin or bivalirudin study medication was governed by protocol for up to 24 hours, use of open-label heparin was generally not needed. However, the investigators were entitled to manage patients after protocol procedures were completed in a manner consistent with best-available care."

The sponsor indicates that about 21.5% (932/4312) patients in these studies received open-label heparin during the period of protocol observation in these studies. In most cases (about 85%) this heparin was administered at some time after completion of PTCA. The sponsor states that in 99% of these cases, open-label heparin was given without unblinding patients. About half of patients experiencing treatment failure received ancillary open-label heparin. The sponsor's table below summarizes reasons for ancillary open-label heparin.

Table 3: Reasons for Ancillary Open-Label Heparin Given to C92-304 Patients

	BIVALIRUDIN			HEPARIN		
Total Number of Patients	2161	% of total	% of OLH	2151	% of total	% of OLH
Number of Patients Taking OLH	473	(21.9%)		459	(21.3%)	
Reasons for Taking OLH[1]						
Medical treatment after protocol treatment	225	(10.4%)	(47.6%)	225	(10.5%)	(49.0%)
Suspected occlusive events						
Suspected AVC	90	(4.2%)	(19.0%)	79	(3.7%)	(17.2%)
Suspected MI	53	(2.5%)	(11.2%)	47	(2.2%)	(10.2%)
Additional or alternative procedure performed						
Stent Placed	57	(2.6%)	(12.1%)	71	(3.3%)	(15.5%)
Repeat PTCA	29	(1.3%)	(6.1%)	39	(1.8%)	(8.5%)
Arterectomy	15	(0.7%)	(3.2%)	17	(0.8%)	(3.7%)
CABG	11	(2.3%)	(2.3%)	24	(1.1%)	(5.2%)
Urokinase Given	4	(0.2%)	(0.9%)	7	(0.3%)	(1.5%)
Procedural difficulties or complications						
Technical Difficulties	53	(2.5%)	(11.2%)	52	(2.4%)	(11.3%)
Failed to Cross Lesion	11	(0.5%)	(2.3%)	18	(0.8%)	(3.9%)
Clinical adverse event						
Chest Pain	32	(1.5%)	(6.8%)	26	(1.2%)	(5.7%)
Other adverse event	9	(0.4%)	(1.9%)	17	(0.8%)	(3.7%)

[1]*Note.* Patients may have more than one reason for being given ancillary open-label heparin

sponsor's table, 1/7/00 briefing document

The sponsor reports that most of the ancillary open-label heparin was given "as continuation of heparin infusion after completion of the protocol" consistent with normal care. In addition to for continuation of anticoagulation, other reasons for open-label heparin included suspected occlusive events, additional or alternative procedures, procedural difficulties or complications, and clinical adverse events including chest pain or hemorrhage. [Note: Some of the sponsor's numbers in the table above are a bit different from those obtained using the submitted databases, e.g., number of bivalirudin patients taking open-label heparin (OLH) in this table is 473; based on the datasets this should be 436].

The sponsor's table below summarizes event rates for patients receiving ancillary heparin in these studies.

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Table 2: Protocol Defined Study Endpoints in Patients Given Ancillary Open-Label Heparin

	BIVALIRUDIN			HEPARIN		
Total Number of Patients	2161	% of total	% of OLH	2151	% of total	% of OLH
Among Total Number of Patients in Trial						
Procedural Failure	160	(7.4%)		177	(8.2%)	
Death, MI, or Revascularization	123	(5.7%)		145	(6.7%)	
Major Hemorrhage	79	(3.7%)		199	(9.3%)	
Number of Patients Taking Open-Label Heparin	473	(21.9%)		459	(21.3%)	
Among Patients Taking Open-Label Heparin						
Procedural Failure	74	(3.4%)	(15.6%)	94	(4.4%)	(20.5%)
Death, MI, or Revascularization	58	(2.7%)	(12.3%)	76	(3.5%)	(16.6%)
Major Hemorrhage	43	(1.9%)	(9.1%)	79	(3.6%)	(17.2%)

sponsor's table, 1/7/00 briefing document

It should be noted that while event rates among patients receiving ancillary heparin were higher in the heparin group than in the bivalirudin group, this table does not tell us whether the events occurred before or after initiation of ancillary heparin.

Reviewer's comments: Use of heparin after discontinuation of study drug continues to be a confounder in Studies C92-3041/2. The following table summarizes clinical event outcome (procedure failure) for patients by whether or not they were exposed to heparin after discontinuation of study drug.

Procedure Failure in Patients with or without Exposure to Heparin after Study Drug Discontinuation

	Procedure Failure* (number of patients, (%))					
	Study C92-304-1			Study C92-304-2		
	total	bivalirudin group	heparin group	total	bivalirudin group	heparin group
Total population	167/2131 (7.8%)	77/1071 (7.2%)	90/1060 (8.5%)	170/2181 (7.8%)	83/1090 (7.6%)	87/1091 (8.0%)
Patients having no post-study heparin@	70/1593 (4.39%)	34/800 (4.3%)	36/793 (4.5%)	108/1851 (5.8%)	57/925 (6.2%)	51/926 (5.5%)
Patients having post study heparin	97/538 (18.0%)	43/271 (15.9%)	54/267 (20.2%)	62/330 (18.8%)	26/165 (15.8%)	36/165 (21.8%)

* protocol definition (death, myocardial infarction, revascularization, abrupt vessel closure)

@ "post-study heparin" = heparin given after study drug treatment discontinued

reviewer's original table, based on personal communication from FDA Biometrics of analysis of data in original NDA submission

In some cases the post-study heparin was given after an endpoint was reached. However, the data suggest that about 80% of patients who received heparin after discontinuation of study drug never experienced a clinical event (procedural failure). Very simply, we do not know what would have happened to these patients had they not received post-study heparin; the post-study heparin may have prevented events in some of these patients. This weakens the argument for equivalence/non-inferiority of bivalirudin to heparin.

In the January 7, 2000 background package submission (Tab 7) the sponsor states, "In more than 95% of patients given open-label heparin, the ancillary treatment was started after completion of key protocol procedures and/or reaching protocol-specified endpoints." It is not clear to me what is meant by 'key protocol procedures'; however, for procedure failure, this statement appears to be at odds with the NDA database. Overall about 5% of patients who received open label heparin after study drug was discontinued had procedure failure after start of open-label heparin. In other words the 95% appears to represent the percentage of patients who received open-label heparin and had procedure failure before the open label heparin was started (about 15% of patients who received open label heparin after study drug discontinuation) plus the patients who received open-label heparin but never had procedure failure (about 80% of patients who received open label heparin after study drug discontinuation).

Using datasets submitted by the sponsor on January 28, 2000 combined with data submitted in the original NDA, the following table of rates of procedure failure for various subpopulations in C92-304-1 and C92-304-2 were derived.

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Procedure Failure in Patients Who Received Open-Label Heparin after Discontinuation of Study Drug

	Procedure Failure* (number of patients, (%))					
	Study C92-304-1		Study C92-304-2		Studies C92-304-1/2 Combined	
	bivalirudin group	heparin group	bivalirudin group	heparin group	bivalirudin group	heparin group
Patients Having Post-Study-Drug heparin, n=	271	267	165	165	436	432
Procedure failure, total	43 (15.9%)	54 (20.2%)	26 (15.8%)	36 (21.8%)	69 (15.8%)	90 (20.8%)
Procedure failure before ancillary heparin	31 (11.4%)	42 (15.7%)	18 (10.9%)	26 (15.8%)	49 (11.2%)	68 (15.7%)
Procedure failure after ancillary heparin	12 (4.4%)	12 (4.4%)	8 (4.8%)	10 (6.1%)	20 (4.6%)	22 (5.1%)
No procedure failure	228 (84.1%)	212 (79.4%)	139 (84.2%)	129 (78.2%)	367 (84.2%)	341 (78.9%)
Post-MI Patients Having Post-Study Drug-Heparin, n=	61	60	27	33	88	93
Procedure failure, total	4 (6.6%)	10 (16.7%)	2 (7.4%)	11 (33.3%)	6 (6.8%)	21 (22.6%)
Procedure failure before ancillary heparin	2 (3.3%)	8 (13.3%)	2 (7.4%)	9 (27.2%)	4 (4.6%)	17 (18.3%)
Procedure failure after ancillary heparin	2 (3.3%)	2 (3.3%)	0	2 (6.1%)	2 (2.3%)	4 (4.3%)
No procedure failure	57 (93.4%)	50 (83.3%)	25 (92.6%)	22 (66.7%)	82 (93.2%)	72 (77.4%)
Non-Post-MI Patients Having Post-Study Drug-Heparin, n=	210	207	138	132	348	339
Procedure failure, total	39 (18.6%)	45 (21.7%)	25 (18.1%)	25 (18.9%)	64 (18.4%)	70 (20.6%)
Procedure failure before ancillary heparin	29 (13.8%)	35 (16.9%)	17 (12.3%)	17 (12.9%)	46 (13.2%)	52 (15.3%)
Procedure failure after ancillary heparin	10 (4.8%)	10 (4.8%)	8 (5.8%)	8 (6.1%)	18 (5.2%)	18 (5.3%)
No procedure failure	171 (81.4%)	162 (78.3%)	113 (81.9%)	107 (81.1%)	284 (81.6%)	269 (79.4%)

* protocol definition (death, myocardial infarction, revascularization, abrupt vessel closure)

reviewer's original table, based on calculations using data in original NDA and 1/28/00 submission (personal communication, FDA Biometrics)

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
ADDENDUM TO MEDICAL OFFICER'S REVIEW

NDA:	NDA 20-873 (BZ)(3/3/99) NDA 20-873 (BZ)(8/5/99) NDA 20-873 (N-200, YY)
Sponsor:	The Medicines Company One Cambridge Center Cambridge, Massachusetts 02142
Drug name:	Hirulog (bivalirudin) Injection
Date submitted:	March 3, 1999 August 5, 1999 January 26, 1999
Date received:	March 5, 1999 August 9, 1999 January 28, 1999;
Review completed:	September 28, 1999
Addendum completed:	January 10, 2000
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Correction of typographical error:

In my Medical Officer's Review of this NDA dated October 6, 1999:

1. On page 1, 6th line of 3rd paragraph "p=0.001" should be "p=0.018".

2. On page 2, last column of the table titled, Summary of Results from Study C92-304-1 and Study C92-304-2, for Study C92-304-2 p-value should equal "0.018" instead of "0.001".

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 1/10/00

cc:
NDA 20-873
HFD-180/Division File
HFD-180/LTalarico
HFD-180/SAurecchia /S/ 1-10-00

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	NDA 20-873 (BZ)(3/3/99) NDA 20-873 (BZ)(8/5/99)
Sponsor:	The Medicines Company One Cambridge Center Cambridge, Massachusetts 02142
Drug name:	Angiomax (Hirulog; bivalirudin) Injection
Date submitted:	March 3, 1999 August 5, 1999 January 26, 1999
Date received:	March 5, 1999 August 9, 1999 January 28, 1999
Review completed:	September 28, 1999
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
Angiomax (Hirulog; bivalirudin) is a homogeneous synthetic 20-amino acid peptide which is a direct thrombin inhibitor active against both clot-bound and circulating thrombin. The sponsor is seeking approval of bivalirudin for use as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

An NDA for this indication was submitted December 23, 1997. The clinical evidence for efficacy consisted of two multi-center, double-blind, active controlled (heparin) trials of identical design in patients with unstable angina who were undergoing PTCA (Studies C92-304-1 and C92-304-2). Though heparin is not approved for use in PTCA, it is commonly used for anticoagulation during the procedure. The trials were designed to demonstrate superiority of bivalirudin over heparin with a protocol specified composite endpoint of "procedural failure" (comprised of death, myocardial infarction, urgent revascularization and abrupt vessel closure during hospitalization) as the primary efficacy parameter.

A total of 2131 patients were randomized and treated in Study C92-304-1 and 2181 patients in Study C92-304-2. Both studies failed to demonstrate superiority of bivalirudin over the heparin comparator with regard to the primary efficacy endpoint. In one study (C92-304-2) the stratum of patients having history of myocardial infarction within 2 weeks prior to study entry (post-MI patients) showed significantly lower rates of procedural failure in the Hirulog group as compared to the heparin group ($p=0.001$). However, this result was not replicated in Study C92-304-1 ($p=0.104$). (See Medical Officer's Review, K. Robie-Suh, dated 10/6/98).

Safety analyses showed significantly fewer bleeding events, both major and minor, in the bivalirudin group as compared to the heparin group in both studies.

These results are summarized in the following table for all patients and for post-MI population:

Summary of Results from Study C92-304-1 and Study C92-304-2

	All Patients			Post-MI Patients		
	bivalirudin	heparin	p-value	bivalirudin	heparin	p-value
Study C92-304-1:						
Procedural failure*	77/1071 (7.2%)	90/1060 (8.5%)	0.253	10/206 (4.9%)	18/203 (8.9%)	0.104
Any bleeding event	593/1071 (55.4%)	864/1060 (81.5%)	<0.001	118/206 (57.3%)	151/203 (7.4%)	<0.001
Major bleeding event	47/1071 (4.4%)	113/1060 (10.7%)	<0.001	8/206 (3.9%)	25/203 (12.3%)	0.002
Study C92-304-2:						
Procedural failure*	83/1090 (7.6%)	87/1091 (8.0%)	0.796	9/163 (5.5%)	22/169 (13.0%)	0.001
Any bleeding event	561/1090 (51.5%)	835/1091 (76.5%)	<0.001	78/163 (47.9%)	115/169 (68.0%)	<0.001
Major bleeding event	32/1090 (2.9%)	86/1091 (7.9%)	<0.001	1/163 (0.6%)	19/169 (11.2%)	<0.001

* procedural failure: death, myocardial infarction, revascularization or abrupt vessel closure; p-values for procedural failure from sponsor's tables (See my MOR dated 10/6/98, pp. 31 and 53); p-values for bleeding, Fisher's exact test

reviewer's table

The NDA was presented and discussed at a meeting of the Cardiovascular and Renal Drugs Advisory Committee on October 23, 1998. Several issues were discussed in great detail. Major ones included:

- *use of heparin in patients entered into these studies:* Conventionally, patients with unstable angina are treated with intravenous heparin. Most of the patients in these studies received some non-study heparin either before and/or after the PTCA procedure. About 25% of patients had received heparin within 1 hour prior to start of the procedure.
- *changes in medical practice with regard to PTCA since the pivotal studies were conducted (4/93-4/95):* Major changes include: (1) sheath removal the same day of the procedure in most cases, whereas in the studies sheaths were kept in place overnight with infusion of study drug being continued for up to 24 hrs (mean, about 16hrs; median, about 18hrs), (2) introduction of stents and the much lower likelihood of abrupt vessel closure, which may be predominantly a mechanical event rather than a thrombotic event, and (3) introduction of glycoprotein IIB/IIIA inhibitors as adjunctive therapy in PTCA.
- *inability to assert noninferiority of bivalirudin to the comparator:* The efficacy studies as sized were intended to demonstrate superiority of the bivalirudin arm. They were inadequately powered to demonstrate, convincingly, noninferiority (a difference of up to 33% between treatments could exist in the actual rate of protocol defined procedure failure in the population). [See pages 144-146 and 239 of Advisory Committee transcripts], and
- *uncertainty as to how much of the difference in the hemorrhage rate between groups is due to the protocol as opposed to how much is due to a true difference between the drugs:* It is possible that the occurrence of bleeding events in the heparin group, particularly after completion of the PTCA, may have been driven by the fact that heparin was not monitored with aPTT as is conventionally done in practice. Also, the heparin regimen used in the studies was more aggressive than what is conventionally used.

Citing deficiencies in these areas, the Advisory Committee voted 5 to 3 against recommending approval of bivalirudin for use as an anticoagulant in patients undergoing PTCA who have unstable angina.

The sponsor was issued a non-approval letter for the NDA application on November 18, 1998 citing failure to demonstrate a benefit of bivalirudin over the comparator for the primary efficacy endpoint, procedural failure. The observed lower bleeding rate in the bivalirudin patients was acknowledged; however, the safety benefit may have resulted from the heparin regimen used as comparator and the lack of customary monitoring of aPTT in patients during the period of study drug administration. A number of Chemistry, Manufacturing and Controls deficiencies also were identified.

Regarding clinical issues, the sponsor was advised to consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of bivalirudin, compared to heparin, in post-MI patients undergoing PTCA for the treatment of unstable angina. In addition, the sponsor was advised to assess the pharmacokinetics, pharmacodynamics, and safety of bivalirudin in patients with renal impairment.

The clinical deficiencies were discussed in a meeting of the Division with the sponsor on January 15, 1999. In the current submission the sponsor presents:.

- a summary of clinical effects of bivalirudin consisting of:
  - analysis and meta-analysis of results from two Phase II dose-ranging studies in PTCA (Study C90-041) and unstable angina (TIMI-7 study) previously submitted to the NDA., and
  - discussion and analyses estimating the clinical effects of bivalrudin and heparin compared to an "imputed placebo" in PTCA.
- a review of evidence supporting the view that bivalirudin is associated with less hemorrhage than heparin in PTCA for unstable angina with particular emphasis on potential confounding.
- new analyses pooling results from Study C92-304-1 and Study C92-304-2

The material submitted by the sponsor is summarized and discussed below.

Clinical Effects of Bivalirudin

A. *Support for a dose-response relationship for bivalirudin:* The sponsor presents a meta-analysis of two dose-response trials of bivalirudin, namely C90-041 (Topol study) and C92-301 (TIMI-7).

Study C90-041 (Topol) was an open-label, multicenter, dose-ranging study of bivalirudin in 291 patients undergoing PTCA. This study was discussed in my Medical Officer's Review dated 10/6/98. In this study the dosing regimens (consisting of a bolus followed by infusion) were changed several times during the study. This study is cited as providing the dose to be studied in the Phase III studies (C92-304-1 and C92-304-2); however, it is not clear from the study report exactly how the dose chosen was derived from the data gathered in this study. Of the 289 patients dosed in this study only 12 received the bivalirudin dose ultimately chosen for use in the Phase III studies. Though there was some evidence for a dose/response effect on aPTT, PT and ACT over the range of bivalirudin doses used in Study C90-041, there was not a clear dose response with regard to proportion of patients with unsuccessful angioplasty. Angioplasty results and ACT values for patients in this study are summarized in the following table:

Summary of Results from Study C90-041

Bolus (mg/kg) Infusion (mg/kg/hr)[a]	0.15 0.6	0.25 1.0	0.35 1.4	0.45 1.8	0.55 2.2	1.00 2.5
No. of patients dosed	57	50	45	73	54	12
No. of patients evaluated	52	44	41	70	51	12
Patients (%) achieving ACT >300sec	12%	26%	50%	72%	84%	100%
No. of patients with unsuccessful angioplasty[b]	3 (6%)	5 (11%)	6 (15%)	3 (4%)	2 (4%)	0 (0%)

[a] There was adjustment in infusion rates in some patients based on ACT levels and the number and timing of coagulation studies was modified during the study. Infusion was to contintue during PTCA and post PTCA "up to 24 hours after start of (bivalirudin) administratrion, at the discretion of the investigator." Actual infusion times ranged from 4 hrs -24 hrs.

[b] Unsuccessful angioplasty included patients with AVC and complications of AVC (including in-hospital death, MI, and emergency revascularization). MI was not defined.

reviewer's table, based on information in NDA Vol. 1.49, p. 149 and Vol. 1.66, p. 4 and 154 through 180, p. p. 200, p. 265 and p. 270

The sponsor pooled the three lowest doses to create an "inactive group" and the three highest doses to create an "active group". The sponsor's results for unsuccessful angioplasty comparing these two groups are shown below:

Table 3. Study C90-041 In PTCA: Incidence Of Death, MI, Revascularization Of Angiographic Evidence Of Abrupt Vessel Closure During Hospitalization

EVENT	INACTIVE DOSES GROUPS 1-3	ACTIVE DOSES GROUPS 4-6	P-VALUE
All patients	152	139	
Median procedural ACT (5, 95%)	241 (171, 334)	314 (243, 405)	<0.001
ACT >300 seconds for procedure	42 (27.9%)	110 (79.1%)	<0.001
Death, MI, revasc., AVC	19 (12.5%)	5 (3.6%)	0.006
Completed PTCA	137 (91.1%)	133 (95.7%)	0.068
Patients completing PTCA (n)	137	133	
Death, MI, revasc., AVC	14 (10.2%)	5 (3.8%)	0.038

sponsor's Table 3, NDA Vol. 15.1, p. 9

Study C92-301 (TIMI-7) was a randomized, double-blind, multicenter, parallel groups, dose-response study of bivalirudin in 410 patients with unstable angina. The bivalirudin doses used in TIMI-7 were 0.02, 0.25, 0.5, and 1.0mg/kg/hr infusion x 72 hrs. Numbers of patients per treatment arm were 165 patients at the 0.02mg/kg/hr dose and 82, 90 and 83 patients at the 0.25, 0.5 and 1.0 mg/kg/hr doses, respectively. The primary efficacy endpoint was defined as the occurrence during 72 hrs of treatment of any of the following: death, "ECG-documented failure of initial therapy" defined as occurrence of "at least a single episode of ischemic pain at rest greater than 5 minutes in duration with documented ECG changes (12-lead) sufficient to satisfy inclusion criteria", or rapid clinical deterioration (other than ischemic

pain) of a patient's status anytime after randomization necessitating emergency angiography/revascularization". In the current submission the 0.02 mg/kg/hr dose is regarded as "putative placebo" and the other three doses as "active". The sponsor's results for this study are shown below:

Study C92-301 in Unstable Angina: Incidence of Death and MI During Hospitalization and Up to 6-Weeks

EVENT (%)	"PLACEBO" DOSE 0.02 MG/KG/H	ACTIVE DOSES 0.25-1.0 MG/KG/H	P VALUE AGE ADJUSTED
	NUMBER OF PATIENTS		
	160	250	
During Hospitalization			
Death or myocardial infarction	16 (10.0)	8 (3.2)	0.009
– Death	4 (2.5)	3 (1.2)	0.439
– Myocardial infarction	12 (7.5)	5 (2.0)	0.023
Up to 6-Weeks After Dosing			
Death or myocardial infarction	20 (12.5)	13 (5.2)	0.014
– Death	8 (5.0)	7 (2.8)	0.286
– Myocardial infarction	17 (11.0)	11 (4.4)	0.026

sponsor's Table 1, NDA Vol. 15.1, p. 7

By this analysis bivalirudin 0.25-1.0mg/kg/hr appeared superior to bivalirudin 0.02mg/kg/hr in preventing "death or MI" or MI alone. [Note: In this analysis 5 patients are excluded from each treatment arm for unspecified reasons].

The sponsor has done a meta-analysis of TIMI-7 and C90-041 for the endpoints death or MI using a random effects model with the following results:

Table 5. Meta-Analysis Of Dose-Response Studies Of Bivalirudin In Unstable Angina And PTCA: Death And MI In Hospital

EVENT	COMBINED ODDS RATIO	95% CI	TWO-SIDED P-VALUE	ABSOLUTE RISK REDUCTION PER 1000 PATIENTS
Death/MI	0.31	0.14, 0.68	0.003	41
– Death	0.42	0.10, 1.81	0.240	8
– MI	0.30	0.12, 0.73	0.009	33

sponsor's Table 5, NDA Vol. 15.1, p. 10

A combined odds ratio of 0.31 (95% CI: 0.14,0.68; p-value 0.003) for bivalirudin as compared to imputed placebo (ineffective doses of bivalirudin) for the combined endpoint of death or MI at about 7 days was obtained. This appears to correlate to an event rate of 7.05% in the "imputed placebo" group and a rate of 2.57% in the bivalirudin group. .(See sponsor's Figure 3, NDA Vol. 15.1, p. 11). It should be noted that for this comparison the

observed effect is stronger in the unstable angina study (event rates of 10.0% for heparin versus 3.2% for bivalirudin) than in the PTCA study (event rates of 3.95% for heparin versus 1.44% for bivalirudin).

Reviewer's comments: Use of TIMI-7 as support for efficacy of bivalirudin in PTCA is limited by several considerations:

- The indication for the TIMI-7 study was unstable angina, not PTCA.
- Impetus for clotting is different for intrinsic insult versus external insult. The balance of clotting factors and responses may not be the same for these two situations. Hence, extrapolation across these studies may not be valid.
- The bivalirudin "active" doses and regimens used in TIMI-7 were not comparable to the regimen used in the PTCA studies. The bivalirudin dose used in the PTCA studies (Study C92-304-1 and Study C92-304-2) was 1 mg/kg bolus, followed by 2.5mg/kg/hr x 4 hrs, followed by 0.2mg/kg/hr X14-20 hrs)]. All three bivalirudin "active" doses in TIMI-7 gave greater total exposure of patients to bivalirudin than did the bivalirudin dosing in the PTCA studies.
- Though the time over which efficacy was assessed for this analysis of TIMI-7 and C92-304-1 and C92-304-2 was "during hospitalization" for all three studies. in TIMI-7 about 45-50% of patients were discharged between 8 and 21 days after initiation of study drug while in Studies C92-304-1 and C92-304-2 the length of hospitalization generally was much shorter (median duration of hospitalization = 4 days; mean = 4.8-5.2 days).

The analyses presented here are all post-hoc and, particularly for the TIMI-7 study, the endpoint used is not that specified in the protocol. In doing these analyses, the sponsor provides no rationale for changing the components of the PTCA procedural failure endpoint being assessed. No comparable analyses using the protocol-specified definition for procedural failure are provided.

The pooling of the data across treatment arms within these studies and across studies for these two different indications is acceptable only as a hypothesis-generating activity.

B. *Support for superiority of bivalirudin over placebo:* The sponsor attempts to support efficacy of bivalirudin over placebo for use in PTCA by: (1) making the case that heparin is effective in PTCA; (2) making the case that bivalirudin is at least as clinically effective as heparin in PTCA, and (3) concluding that, given 1 and 2, bivalirudin is superior to an imputed placebo.

1. Effectiveness of heparin in PTCA: The sponsor provides a discussion of the rationale for use of heparin in PTCA and discusses three observational studies examining procedure failure and the extent of anticoagulation with heparin in PTCA.

   a. Rationale: A number of references describe thrombus formation on arterial catheters (Siegelman, SS et al. Radiology 91:251 (1968); Formanek, G et al. Circulation, 41:833 (1970)). Catheters rapidly become encased in fibrin and clot forms. Thrombus formation during successful angioplasty can be expected to be

exacerbated because the occluding atherosclerotic plaque is torn or fractured producing a deep arterial injury exposing collagen, smooth muscle cells, and elastic tissue, and triggering platelet deposition and thrombus formation. Thrombus formation on catheters can have a number of sequelae. During withdrawal of the catheter the thrombus encasing the catheter can remain fixed on the vessel wall or become mobile being withdrawn with the catheter back to the artery puncture site where they are peeled from the catheter surface and either remain lodged at the puncture site or be washed downstream as emboli. These concerns of embolization and occlusion led to the use of heparin during catheterization procedures.

Use of antiplatelet agents and anticoagulants to limit thrombotic complications during and following angioplasty has evolved empirically with the development of the procedure. Early studies in dogs showed thrombus formation on the surface of catheters left in place in internal jugular veins or carotid arteries for 30 minutes in the absence of systemic anticoagulation, but heparin at a dose of at least 30 units/kg while the catheter was in place was sufficient to eliminate 95 of the surface clot (Nejad, MS et al. Radiology, 91:248 (1968)). Heras et al (Circulation, 78:654 (1988)) showed in pigs showed an inverse relationship between heparin dose in periprocedure period and platelet deposition in carotid arteries with deep injury to the vessel (i.e., a tear through the internal elastic lamina into the media).

Reviewer's comments: Certainly, arterial catherization in the absence of heparin has long been known to result in the formation of thrombi at the puncture site and/or on the catheter in a large percentage of cases. However, clinical evidence of occlusion is much less common than the occurrence of angiographic thrombi. In the Siegelman et al paper (1968) occurrence of a filling defect was found in 56% of 173 patients undergoing diagnostic arteriography (mostly aortic arch and abdominal aortogram studies). Thrombus was $\geq$1mm in 33% (57/173) of patients. However, surgical thrombectomy was indicated in only 2.3% of arteriograms. Similarly, in a study of 93 patients undergoing various procedures including aortography and selective arteriography of coronary, carotid, brachial, celiac, renal, or iliac arteries Formanek et al (1970) noted thrombus formation in 54% (50/93) of patients, but only 8 patients developed a pulse deficit and of these only 2 required intervention. (Pulse returned spontaneously in 5 patients and 1 patient was asymptomatic).

Formation of clots appears to be affected significantly by duration of the procedure with longer catherization time giving more thrombus formation. Formanek et al (1970) found thrombus formation in 39% (15/38) of patients in whom the catheter was in place for $\leq$30 minutes but in 65% (20/31)of cases where the catheter was in place for >30 minutes. (However, thrombus formation was noted as early as 15 minutes after introduction of the catheter). In Studies C92-304-1 and C92-304-2 in this NDA for most patients the PTCA procedure lasted <30 minutes.

Also, it should be remembered that use of systemic heparinization brings along with it the increased risk of serious and/or fatal hemorrhage, particularly in the event of inadvertent vascular or cardiac perforation.

b. Procedure failure and extent of anticoagulation with heparin in humans: The sponsor discusses three papers from the literature.

Narins (Narins, CR et al. *Circulation 93*:667 (1996)) describes a case control study to evaluate the relation between activated clotting time (ACT) during angioplasty and abrupt vessel closure in these patients. The paper was written in 1995 and published in 1996. Records for 1290 patients undergoing angioplasty at Duke University Medical Center from July 1, 1989 through December 31, 1990 were examined. All patients had received aspirin before and after angioplasty and heparin during the procedure. Heparin was given as one or more boluses. No patients received continuous heparin infusions during the procedure. However, after the procedure most patients were anticoagulated with heparin overnight and had their vascular sheaths removed the following morning. No further description of the total angioplasty population is provided. Rather two subpopulations were identified: (1) patients suffering abrupt vessel closure (AVC) and who had ACT data available and (2) a "control group" consisting of 124 randomly selected patients (2 for each AVC patient) who had ACT data available and who matched the AVC group with regard to preprocedural total vessel occlusion, unstable angina, and lesion location.

The authors identified a total of 76 (5.9%) patients who had suffered AVC as determined by either: (1) total occlusion (TIMI grade 0 or 1 flow) of the dilated artery at any time during the procedure or (2) repeat catheterization before hospital discharge that showed total occlusion of the previously dilated lesion or subtotal occlusion with ECG evidence of ischemia. For the patients who experienced AVC, 62 (81.6%) had 1 or more measurements of activated clotting time (ACT) available. Demographic features of these patients included a median age of 60 years, 69% male, 92% white, and 11% had diabetes mellitus. With regard to coronary artery disease, 21% had unstable angina, 13% had total occlusion of the target vessel, 63% had single vessel disease and 21% had 2-vessel disease. Mean initial stenosis was 91% and initial TIMI flow was 3 in 85% of these patients. Target lesion was LAD in 43% of patients and RCA in 34%. Sixty-five percent of these patients (40/62) had received heparin prior to coming to the angioplasty laboratory. The control group was similar in most regards except that there were fewer patients who had had heparin prior to coming to the angioplasty laboratory and there were somrewhat more patients with diabetes mellitus.

Among the 62 patients in the AVC group, 21 suffered acute MI, 23 required emergency coronary artery bypass graft (CABG) surgery and 2 died. MI was defined as either: (1) new Q waves ($\geq$0.04msec wide) in 2 or more contiguous leads, (2) total CK increased to > 2x upper limit of normal with MB fraction > 5%, or (3) total CK-MB > 20 IU/L (2x upper limit of normal) with new ischemic changes on ECG.

"Initial" ACT values were measured 5 to 10 minutes after the last pre-procedural bolus of heparin in the angioplasty laboratory. Most patients received only 1 heparin bolus while in the angioplasty laboratory and most (68%) had only 1 ACT checked. Patients in the control group had significantly lower ACT values than did those who suffered AVC (control group: median ACT = 380 sec, 25th percentile = 335 sec, 75th percentile = 423sec); AVC group: median ACT = 350sec,

25th percentile = 309 sec, 75th percentile = 401sec [normal value 126 ± 13 sec]). Also, minimum in-lab ACT values were lower in the AVC group than in the control group. The author determined that there appeared to be a fairly linear inverse relationship between ACT and probability of AVC. By the sponsor's analysis, pre-procedural heparin (before coming to the angiography lab) did not affect the result.

The occurrence of bleeding requiring transfusion was more common in the control group than in the AVC group (21% vs. 8.9%)

Reviewer's comments: The result of this case control study is useful as a hypothesis generating investigation. There are several problems with using this study to draw conclusions about the effect of anticoagulation in the total population of patients undergoing PTCA.

- First, neither the treatment given to the patients (extent of anticoagulation) nor the monitoring done was randomly assigned. The interventions were made as conscious decisions on the part of the treating-operating physician(s) utilizing their entire medical knowledge for each patient. The heparin treatment and monitoring are likely to have been done in a highly selective fashion. There is considerable overlap in ACT values for the AVC and control groups. It is not obvious that the outcome for any patient would have been different had the ACT been higher.

- Second, the number of patients included in the control group was arbitrary and represented only 10.2% of the potential control population while the AVC group consisted of all identified cases in the population. Hence, it is likely that the control patients are a highly selected group.

- Third, the paper states that: "All patients who matched the case patients [on predictors of AVC] were identified , then two matching control subjects were randomly chosen for each case." However, no information is given as to how many of the non-AVC patients potentially matched AVC patients or the exact procedure for the matching.

- Finally, the handling of anticoagulation during PTCA in this paper does not reflect current medical practice where there is frequently periprocedural use of a low molecular weight heparin in patients with angina (Lovenox) and where use of other agents such as monoclonal antibodies (e.g, abciximab [ReoPro]) may be used during the procedure.

This paper suggests a correlation between ACT level and occurrence of AVC; however, causality cannot be ascertained. The hypothesis should be tested in an appropriately designed prospective clinical trial.

The paper by Ferguson (Ferguson et al., JACC 23:1061 (1994)) is another case control study. The author examined all the coronary angioplasty procedures done from October 1988 to October 1989 at St. Luke's Episcopal Hospital, Houston, Texas. Of 1,469 procedures done 103 patients (7%) underwent urgent or emergency CABG or died. All patients received an intravenous bolus of heparin

10,000 U prior to start of the procedure and ACT was measured. Additional heparin was given and ACT measured at the discretion of the physician/operator. A "control group" consisting of the first 400 patients who underwent PTCA during this time but did not have complications (i.e.,urgent/emergent CABG and/or death) was identified. Demographic features of the two groups were similar, but the group with complications tended to be sicker (more recent MI's, more NYHA Class IV patients, more recent thrombolysis patients, more type C lesions, and more patients on heparin infusion prior to PTCA). ACT values after heparin therapy for the two groups are summarized in the following table:

Activated Coagulation Times after Heparin Therapy

	ACT after Heparin Therapy (secs)			
	<250	250-275	275-300	>300
N	171	89	151	92
Group I (complications)	63 (61.2%)	21 (20.4%)	11 (10.7%)	8 (7.7%)
Group II (no complications)	108 (27%)	68 (17%)	140 (35%)	84 (21%)

* urgent/emergent CABG and/or death

from author's table, p. 1063

Reviewer's comments: In this case control study there is an inverse correlation between the ACT after heparin bolus and prior to PTCA and the occurrence of complications. In this study though all patients presumably received the same bolus dose of heparin, there resulted a wide range of ACT values. The author questions the predictive value of the observed correlation. He states:

> "...the final activated coagulation time measurements may reflect events that transpired in the catherization laboratory, which, in turn, may have resulted in adverse events as well as in affecting the total dose of heparin administered. We noted a number of circumstances where abrupt vessel closure in the catheterization laboratory is accompained by a precipitous decrease in activated coagulation time. Low final activated coagulation times may reflect an ongoing thrombotic process (perhaps initiated by in-laboratory complications) or inadequate heparinization, or both. The activated coagulation time after heparin therapy and the activated coagulation time response to an initial bolus of heparin are associated with complications after coronary angioplasty. However, a low activated coagulation time after heparin therapy and a diminished heparin response may also reflect antecedent clinical events, and rather that being an independent risk factor, impaired heparin response may be a secondary manifestation of the underlying clinical state." (Ferguson et al paper, p. 1064)

In short the study does not answer the question: Do patients have complications because their activated coagulation times are low, or are their activated coagulation times low because they have complications? In fact, there is some information in the literature suggesting that there may be heparin resistance among cardiovascular patients, with unstable angina patients having less of an anticoagulant response to a heparin than patients with stable angina (Ogilby, JD et al Cath. Cardiovasc. Diag. 18:206 (1989)).

The McGarry paper (McGarry et al., Amer. Heart J. 123:1445 (1992)) describes the relationship of partial thromboplastin time (PTT) to outcome in 487 patients who underwent elective PTCA from January 1, 1988 to December 31, 1988. A total of 487 patients who underwent elective PTCA were identified. The procedure was successful in 453 (95%) of these patients (i.e., residual stenosis of the lumen of the treated vessel was $\leq$50%). Of the successfully treated patients, 336 had PTT recorded in the patient chart.

All patients in this report received a heparin bolus of 10,000 U at the beginning of PTCA, followed by a continuous infusion of heparin at 2000 U/hr which was reduced to 1000 U/hr after PTCA procedure was completed. This was continued for 18-24 hrs until prior to removal of the femoral access sheath. Patients received aspirin (81mg) before and daily after the procedure. PTT was measured at least 6 hrs after PTCA, at the onset of angina, and before discontinuation of heparin for sheath removal.

The 336 patients identified for evaluation were divided into two groups: Group A - patients with PTT $\geq$3 times control value (271 patients) and Group B - patients with PTT<3 times control value (65 patients). The method used to measure PTT reported all values above 150sec as ">150 secs". In group B all values were <75 seconds; in Group A, 48.8% of the values were ">150 secs". Demographic and baseline features for the two groups of patients are not described separately. Overall the mean age was 61 years, 69% were males, 83% had PTCA of a single vessel, and in 50% of patients the artery treated was the LAD. Occurrence of abrupt closure (defined as chest pain with more than 1mm of ST segment elevation on the ECG leads corresponding to the dilated territory associated with an increase in the CK-MB fraction) and ischemic events (defined as chest pain with ST segment shifts on the ECG but no increase in CK-MB) was greater on day 1 and at hospital discharge in Group B than in Group A. There were two deaths in Group B due to complications of abrupt vessel closure and 1 in Group A which was attributed to arrhythmia. Clinical outcomes and complications are summarized in the following table:

Table II. Clinical outcome and complications

	Group A	*Group B*	*p*
N	271	65	
PTT (range in seconds)			
Median PTT (sec)	">150"	62	
Total ischemic complications (day 1)	4 (1.4%)	13 (20%)	<0.001
Total ischemic complications (discharge)	11 (4.0%)	13 (20%)	<0.001
Complications at day 1 (on heparin)			
Abrupt closure	3 (1.1%)	7 (10.7%)	<0.001
Ischemic events	1 (0.8%)	6 (9.2%)	<0.001
Complications at hospital discharge			
Abrupt closure	7 (2.5%)	7 (10.7%)	0.003
Ischemic events	4 (1.5%)	6 (9.2%)	0.001
Transfusion	8 (2.9%)	3 (4.6%)	NS
Death	1 (0.4%)	2 (3.0%)	NS

NS, Not significant; *PTT*, partial thromboplastin time.

The following table shows event rates for various PTT ranges in this database:

PTT	Number of Patients with Events (%)
<50	5/15 (33.1%)
50-74	9/50 (18.1%)
75-99	2/56 (3.6%)
100-124	0/33 (0%)
125-150	1/18 (5.5%)
>150	4/164 (8.5%)

reviewer's table, based on information in author's Fig. 1 and Tables III and IV

Reviewer's comments: The most striking aspect of this study is that in spite of all patients presumably receiving the same heparin dose, there was a very wide range in the extent of anticoagulation achieved as measured by PTT. Though there is a suggestion of an inverse correlation between PTT and the occurrence of ischemic complications, patients were unevenly distributed across the PTT range so comparison of the proportions may not be valid. And again, it is not clear that poor anticoagulation response to heparin is an independent risk factor for complications. Impaired heparin response may be a secondary manifestation of the underlying clinical state. No assessment was made of the role of heparinization in the 31% of PTCA patients who had an unsuccessful procedure or who had successful procedure but had no PTT measured.

Reviewer's comments regarding use of heparin in PTCA: The rationale for the use of heparin in PTCA is sound. The intentional injury to the artery produced by balloon dilatation during PTCA denudes the endothelium and causes tears in the intima exposing subendothelial tissue factor and extracellular matrix to blood thereby generating thrombin which activates platelets and results in thrombosis. It stands to reason that agents which work against clotting should be helpful in preventing the undesirable effect of clotting at the site of angioplasty. The dog and pig studies discussed above support that systemic heparin decreases formation of thrombus on catheters.

There is an abundance of literature attesting to the widespread use of heparin for anticoagulation during PTCA for the past 20 years. However, what is not widespread is the acceptance of any particular dosing regimen including bolus dose (if any), infusion dose (if any), or duration of heparin therapy for PTCA. Because of the risk of bleeding with anticoagulation, it is important to minimize the dose for anticoagulants being used in PTCA.

While the three papers presented by the sponsor seek to examine the quantitative relationship between extent of anticoagulation and complications of angioplasty, other studies indicate that very low levels of anticoagulation may be effective. Koch et al (Heart 77:517 (1997)) reported complications in a series of 1375 consecutive patients undergoing elective PTCA from 1/91-12/93 at the Academic Medical Center in Amsterdam. All patients received 300mg aspirin before the procedure and 5000 IU heparin as an intra-arterial bolus after insertion of the arterial sheath. The protocol allowed for an additional dose of up to 2500 IU heparin if the procedure lasted more

than 90 minutes. In most patients the arterial sheath was removed immediately after completion of the procedure. Procedural failure (defined as <50% residual stenosis without death, acute MI, urgent revascularization for failure of angioplasty or repeat angioplasty assessed at 48 hours after start of the procedure) was about 5% In this study. A randomized, double-blind trial in 404 patients (Garachemani, AR et al. Circulation 94:I-198 (1996)) showed a lower failure rate in patients given 5000 U heparin as compared to those given 20,000 U heparin during PTCA (2% for low dose heparin and 7% for high dose heparin); however, 7% of patients in the low dose group and 8% of patients in the high dose group received additional heparin.

It is well-known that a given dose of heparin may exhibit in different individuals a wide range of extent of effect on clotting as measured by aPTT and ACT. It is not clear what dictates the extent of anticoagulation achieved with a dose of heparin in a given individual. Consequently, for the case control studies (Narins paper and Ferguson paper) and the cohort study by McGarry it is not possible to determine whether there is a *causal* relationship between the ACT and procedure failure seen in these studies.

Published PTCA procedure failure rates (variety of definitions, usually including death, MI, revascularization, or symptomatic ECG-documented ischemic events) with use of heparin are tabulated below:

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Published Procedure Failure Rates with Heparin in PTCA

Reference	Study Date	Heparin Dosing	Number of Patients Studied	Procedure Failure[a] Rate
Narins et al (Circulation 93:667 (1996))	7/89 - 12/90	Heparin dose ranged from 10,000-20,750 U during procedure and in most cases heparin was continued overnight till sheath removal.	1290[b]	5.9%
Ferguson et al (J. Am. Coll. Cardiol 23:1061 (1994))	10/88 – 10/89	Bolus of 10,000 U, ACT measured. Additional heparin and ACTs during the procedure at discretion of the operator; not clear whether heparin was continued post procedure..	1469[c]	7.0%
McGarry et al (Am. Heart J. 123:1445 (1992))	1/88 – 12/89	Bolus of 10,000 U followed by infusion of 2,000 U/hr during procedure, then 1,000U/hr for 18-24 hrs till sheath removal	487[b]	7.0%
Koch et al (Heart 77:517 (1997))	1/91-12/93	Bolus of 5,000 U heparin given; additional dose of 2,500U if procedure lasted >90min. Sheath removed immediately after procedure[d]	1375[b]	about 8-10%
Garachemani, AR (Circulation 94:I-198(Abs)(1996))	not given	Pts randomized to low dose heparin (5,000U) bolus or high dose heparin (20,000U) bolus during PTCA. Arterial sheaths removed 4 hrs after the procedure.	404[c]	2%, low dose heparin; 7%, high dose heparin
Garachemani, AR et al (Am Heart J. 136:352 (1998)	not given	Bolus of 5,000-20,000 U during procedure; pts randomized to continued heparin 1,000U/hr for 12-20 hrs till sheath removal or no continued heparin and sheath removed 3-4 hrs after procedure.	100[c] (continued heparin) 91[c] (no continued heparin)	3 pts (3%) in the continued heparin group had AVC and MI; all three had stents 4pts (4%) in the no continued heparin group had MI; 1 pt died. No pts underwent CABG.

[a] Definition of this endpoint was not the same among all studies; however, in each study this is what was assessed to be clinically meaningful events.
[b] All patients received aspirin.
[c] Aspirin use not reported.
[d] 8.9% of pts required continued heparin overnight because of: dissection, "bail-out" stenting, suboptimal result, temporary occlusion, occluded side branch, presence of thrombus or other reason. About a third of these (45 of 123 pts) still suffered acute ischemic complications.

reviewer's original table

No true placebo rates for procedure failure in PTCA are available. Study C92-041 showed a procedure failure rate of 6% (3/57) for the lowe t bivalirudin dose, 11% (5/50) for the next highest dose, and 15% (6/45) for the next highest dose, suggesting that procedure failure is likely to be affected by factors in addition to anticoagulation. In the absence of a placebo control it is not possible to tell in a given study whether the observed procedure failure rate is most influenced by those other factors or by anticoagulation. Hence, making an equivalence or "no worse than" claim for bivalirudin for clinical effect of anticoagulation based on no difference between heparin and bivalirudin in Studies C92-304-1 and C92-304-2 in the absence of an anticoagulation placebo is not valid.

Recently, the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy has recommended the following with regard to heparin use in PTCA:

> Heparin should be given in sufficient doses to achieve an ACT of 250 to 300 s with the HemoTec device and 300 to 350 s with the Hemochron device. This is a grade C1 recommendation for heparin use and a grade B1 recommendation for the level of ACT-guided anticoagulation. Weight-adjusted heparin boluses (70–150 IU/kg) or sex-adjusted heparin boluses (7,000 IU for women; 8,000 U for men) can be used to avoid excessive levels of anticoagulation. If the desired ACT is not achieved after a bolus of heparin, additional heparin boluses (2,000 to 5,000 U) can be administered. Routine postprocedural infusion of heparin is not recommended. These grade C1 recommendations are based on results of four level III trials.[12,13,55,73] Early sheath removal when the ACT falls to less than 150 to 180 s is recommended to reduce the incidence of complications at the access site.
>
> **Popma, JJ et al. CHEST 1998; 114:728S**

(Note: The notation of a Grade C1 recommendation indicates that it is based on "weak methods – observational studies, but the effect is clear that benefits do outweigh the risks". The Grade B1 recommendation indicates that the methods are strong (randomized controlled trials, heterogeneity present; but the effect is clear that benefits do outweigh the risks. Level III trials are nonrandomized concurrent cohort studies).

Routine use of heparin after completion of uncomplicated PTCA is not recommended (a Grade B1 recommendation based on two randomized controlled trials (Friedman, HZ et al J. Am. Coll. Cardiol 24:1214 (1994); Ellis, SG et al Am. Heart J. 117:777 (1989)). Additional recommendations have been made regarding use of GPIIb-IIIa receptor antagoninsts with heparin. Pretreatment with aspirin is also recommended. [The full recommendations of the ACCP for coronary angioplasty are attached to this review as Appendix A].

Heparin (which has been marketed since 1917) is not labeled for use in PTCA. No application for heparin for this indication ever has been submitted. A study which prospectively targets and brings a large series of patients to a prespecified expected-to-be-adequate extent of anticoagulation could be useful in supporting directions for

heparin use in PTCA if the procedural failure rate in the study approaches 0% and the bleeding rate is acceptable.

2. Bivalirudin is at least as clinically effective as heparin in PTCA: The sponsor uses new analyses of clinical trials C92-304-1 and C92-304-2 to support that bivalirudin is not worse than heparin in PTCA. No new data are submitted.
In the new analyses the sponsor has made several changes in definitions of parameters. These include:
   a. The primary efficacy parameter has been changed. By the protocol and in the study report the primary efficacy parameter was a composite consisting of death, MI, revascularization and abrupt vessel closure (AVC). The sponsor's new primary efficacy endpoint consists only of death, MI and revascularization. AVC is excluded as a component. The sponsor states: "Determination of AVC was subjective and relied on interpretation of subtle angiographic findings by individual treating physicians. Angiographic AVC often cannot be confirmed upon independent review. For this reason, protocols for antithrombin or antiplatelet drugs no longer use AVC as an endpoint."
      [Reviewer's note: AVC was numerically the most common endpoint event reported by investigators in these studies. This event was certainly of clinical importance in that it almost always resulted in an intervention (usually stenting). Most often this intervention appears not to have been captured in any of the other efficacy endpoint assessments. By my counts in C92-304-1 about 44 bivalirudin patients and 45 heparin patients had stents placed; in C92-304-2 about 26 bivalirudin patients and 35 heparin patients had stents placed].

   b. The definition of myocardial infarction has been revised. The protocol specified that clinical efficacy endpoints (including MI) would be adjudicated by a 5 member Morbidity and Mortality Classification Committee using the following definition: "Myocardial infarction is defined as the presence of at least two of the three following criteria: (1)prolonged angina (>30 minutes); (2) total creatinine kinase elevation $\geq$2 x upper limits of normal and CK-MB $\geq$4%; (3) new development of 2 step Minnesota Q wave* codes or new left bundle branch block (not rate related)." *[Reference: Blackburn, H. et. al. J. Electrocardiol. 2:305 (1969)]. The sponsor's new definition of MI is shown in the following table:

Core Laboratory Definitions of MI Used in Revised Analysis of Pivotal Studies

Core Laboratory Code	Patient Symptoms	ECG	Cardiac Enzymes
1		New 2 grade Q wave worsening of the Minnesota code	
2	Chest pain >30 minutes	New ST- or T-wave abnormalities	Elevation of CK-MB beyond 2x ULN (regardless of total CK level)
3		New ST- or T-wave abnormalities	Elevation of CK-MB beyond 2x ULN (regardless of total CK level)
4	Chest pain >30 minutes	New ST- or T-wave abnormalities	Equivocal enzymes
6			Elevation of CK-MB beyond 2x ULN (regardless of total CK level)
9	Chest pain >30 minutes	New left bundle branch block	Elevation of CK-MB beyond 2x ULN (regardless of total CK level)

sponsor's table NDA Vol. 15.1, p. 20

c. The primary efficacy endpoint is assessed for the period 7 days or to end of hospitalization (whichever came first) rather than for "during hospitalization" as specified in the protocol.

Using the new endpoint criteria, for Studies C-92-304-1 and C-92-304-2 combined a total of 71 bivalirudin patients (3.3%) and 90 heparin patients (4.2%) suffered myocardial infarction during the first 7 days in hospital. (Numbers were not given for the two studies separately). [An additional 2 bivalirudin patients and 1 heparin patient suffered new definition MI while in hospital but after day 7]. (See NDA Vol. 15.1, p. 21 and NDA Vol. 20.5, response to Clinical Question 1). In the clinical study report in the original NDA submission there were 44 patients (2.0%) with MI in the bivalirudin group (21 (2.0%) in C92-304-1; 23 (2.1%) in C92-304-2) and 52 patients (2.4%) with MI in the heparin group (28 (2.6%) in C92-304-1; 24 (2.2%) in C92-304-2). The sponsor indicates that the data on which the patients were reclassified for MI were collected at the same time as the other study data and have not been changed since the database for the study was locked.

Using the new definitions the sponsor analyzed (revised) procedure failure in Study C92-304-1 and Study C92-304-2 individually and separately obtaining the following results:

Summary of Results from Sponsor's Efficacy Analyses of Revised Primary Endpoint

	Number patients with revised procedural failure (%)*		p-value*	odds ratio (95%CI)
	bivalirudin	heparin		
Study C92-304-1	69/1071 (6.4%)	84/1060 (7.9%)	0.208	0.80 (0.57-1.11)
Study C92-304-2	66/1090 (6.0%)	85/1091 (7.7%)	0.129	0.77 (0.55-1.07)
Meta-analysis C92-304-1/2	135/2161 (6.2%)	169/2151 (7.8%)	0.043	0.78 (0.62-0.99)

* revised procedural failure = death, MI (revised definition) and revascularization up to 7 days (or end of hospitalization)
* Fisher's exact test

from sponsor's table, NDA Vol. 20.5, response to Statistical question #2

This result is not much influenced by time at which the revised endpoint is assessed (5 days, 7days, 8 days or "in hospital") or by the change in MI definition. However, statistical significance in the meta-analysis is lost if AVC is included in the endpoint. (See NDA Vol. 15.2, pp. 340 through 349 and Vol. 20.5, response to statistical question 2). No analysis showed a statistically significant benefit of bivalirudin over heparin in either of the studies individually, though each study showed a numerical trend in favor of bivalirudin in these analyses for the overall population. For the post-MI and non-post MI subgroups, as was the case in the sponsor's previous analyses of the individual studies, the meta-analysis also failed to show statistically significant superiority of bivalirudin over heparin in the non-post-MI subgroup; a benefit was seen in the post-MI subgroup [odds ratio of 0.47 (95% CI, 0.26-0.84) for post-MI patients and 0.87 (95% CI, 0.67-1.13) for non-post-MI patients].

Results of the new analyses did not appear to be significantly affected when examined for effect of age (<65 years vs. ≥65yrs), baseline weight above median weight, use of nitrates, or impaired renal function (GFR<60ml/min). Female post-MI patients, particularly those on heparin, appeared to have more major bleeding events than did males in this group. Post-MI patients with baseline weight below the median weight, particularly those on heparin, appeared to have more procedural failure and "death, MI, or revascularization" than did the overall population or patients with baseline weight above the median weight. Post-MI patients with a history of diabetes treated with bivalirudin appeared to do worse in all regards other than bleeding as compared to the patients in the heparin group.

Because all except 27 patients in these two studies received aspirin, effect of aspirin use on the result could not be evaluated. Similarly, only a small percentage of patients (192 patients) received warfarin, so effect of warfarin on the result could not be reliably assessed.

The protocol allowed enrollment of patients who had received heparin up to 30 minutes prior to initiation of the study drug and allowed administration of heparin after discontinuation of study drug (which would be after about 18-24 hours following initiation of study drug). The table below summarizes use of non-study heparin before and/or after study drug administration based on information in the original NDA submission.

Use of Non-Study Heparin in Patients During Studies C92-304-1 and C-92-304-2

	Number of Patients (%)					
	All Patients		Non-Post MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Study C92-304-1:						
	N = 1071	N = 1060	N = 865	N = 857	N = 206	N = 203
Heparin administration prior to study drug* (%)	668 (62%)	673 (63%)	493 (57%)	502 (59%)	175 (85%)	171 (84%)
Heparin administration < 1hr before study drug (%)*	211 (20%)	202 (19%)	153 (18%)	147 (17%)	58 (28%)	55 (27%)
Heparin administration < 6 hrs before study drug (%)	621 (58%)	624 (59%)	454 (52%)	462 (54%)	167 (81%)	162 (80%)
Duration of heparin administration prior to study drug > 12 hrs	492 (46%)	476 (45%)	350 (40%)	343 (40%)	142 (69%)	133 (66%)
Heparin administration after discontinuation of study drug (%)	271 (25%)	267 (25%)	210 (24%)	207 (24%)	61 (30%)	60 (30%)
Started on heparin within 8 hrs of discontinuation of study drug	209 (20%)	183 (17%)	162 (19%)	145 (17%)	47 (23%)	38 (19%)
Continued on post- study drug heparin for > 12 hrs	183 (17%)	178 (17%)	142 (16%)	132 (15%)	41 (20%)	46 (23%)
Study C92-304-2:						
	N = 1090	N = 1091	N = 927	N = 922	N = 163	N = 169
Heparin administration prior to study drug* (%)	653 (60%)	720 (66%)	514 (55%)	569 (62%)	139 (85%)	151 (89%)
Heparin administration < 1 hr before study drug (%)	245 (22%)	239 (22%)	193 (21%)	186 (20%)	52 (32%)	53 (31%)
Heparin administration < 6 hrs before study drug (%)	582 (53%)	641 (59%)	456 (49%)	504 (55%)	126 (77%)	137 (81%)
Duration of heparin administration prior to study drug > 12 hrs	489 (45%)	549 (50%)	376 (40%)	424 (46%)	113 (69%)	125 (74%)
Heparin administration after discontinuation of study drug (%)	165 (15%)	165 (15%)	138 (15%)	132 (14%)	27 (17%)	33 (20%)
Started on heparin within 8 hrs of discontinuation of study drug	134 (12%)	113 (10%)	113 (12%)	90 (10%)	21 (13%)	23 (14%)
Continued on post-study drug heparin for > 12 hrs	109 (10%)	109 (10%)	89 (10%)	84 (9%)	20 (12%)	25 (15%)

* includes only patients for whom time of stopping prior heparin infusion was recorded.

reviewer's table, based on sponsor's tables, NDA Vol. 1.112, p. 225 through 228, Vol. 1.124, pp. 192 through 319; NDA Vol. 1.71, pp. 227 through 230 and Vol. 1.85 pp. 175 through 302

There was use of IV heparin prior to study drug in about 58% of non-post MI patients and 85% of post-MI patients in Study C92-304-1 and in 59% of non-post MI patients and 87% of post-MI patients in Study C92-304-2 (generally about .-S hrs before study drug initiation). About 24-30% of patients received heparin after discontinuation of study drug with slightly more post-MI patients receiving post study drug heparin as compared to non-post MI patients. In both studies treatment groups appeared similar with regard to timing of non-study heparin and duration of non-study heparin administration. In both studies most patients received their last non-study heparin between 30 minutes and 6 hours prior to study drug initiation and duration of heparin administration prior to study was greater than 12 hours in the majority of these patients. Most patients who received heparin after discontinuation of study drug were started on heparin within 8 hours of discontinuation of study drug and most of these were continued on heparin for at least 12 hours.

Most of the heparin administration was via the intravenous route. In Study C92-304-1 only 7 Hirulog patients and 14 heparin patients received heparin subcutaneously. In Study C92-304-2 only 19 Hirulog patients and 29 heparin patients received heparin subcutaneously.

The sponsor's tables below show the efficacy result for patients who did not receive heparin before or after the study drug. Procedural failure in these tables is the protocol specified definition (includes death/MI/revascularization/AVC).

Table C2.1 Incidence of Prpcedural Failure and components of procedural failure (including protocol defined MI) at in hospital up to 7 days in patients with no pre or post study drug heparin. Studies C92-304-1/2 combined

	BIVALIRUDIN N=167	HEPARIN N=157
Procedural Failure	30 (18%)	26 (16.6%)
Death/MI/Revascularization	23 (13.8%)	23 (14.6%)
Death/MI	11 (6.6%)	11 (7%)
Death	1 (0.6%)	0
MI	10 (6%)	11 (7%)
Revascularization	16 (9.6%)	18 (11.5%)

Table C2.2 Incidence of Procedural Failure and components of procedural failure (including Core-laboratory definition of MI) at in hospital up to 7 days in patients with no pre or post study drug heparin. Studies C92-304-1/2 combined

	BIVALIRUDIN N=167	HEPARIN N=157
Procedural Failure	34 (20.4%)	31 (19.7%)
Death/MI/Revascularization	27 (16.2%)	28 (17.8%)
Death/MI	15 (9%)	17 (10.8%)
Death	1 (0.6%)	0
MI	15 (9%)	17 (10.8%)
Revascularization	16 (9.6%)	18 (11.5%)

sponsor's tables NDA Vol. 20.5, response to clinical question 2

The procedure failure rate in these patients appears similar for the two treatment groups but higher than was seen in the overall population. For the individual components of procedural failure, abrupt vessel closure (AVC) was higher in the bivalirudin group (7 patients) as compared to the heparin group (3 patients).

It should be noted that in this analysis the number of patients included as having not received heparin before or after study drug (about 7.5% of patients) is smaller than would be expected based on the information in the original NDA (not less than 17% of patients). The data listings in the original NDA included post-study treatment heparin in the list of concomitant medications and the listing of patients not receiving prior or post study heparin included in the sponsor's response to clinical question 2 did not present prior- and post-study heparin use separately; so, the reason for the discrepancy cannot be examined using the available database. Regardless, it appears that prior and post-study use of heparin was sufficiently widespread as to introduce a significant confounding factor into the interpretation of the study results.

Finally, the sponsor also has done a "meta-analysis" of bivalirudin versus heparin in "ischemic heart disease" combining results from trials in unstable angina/non Q-wave MI (C93-309 [TIMI-8]), PTCA (C92-304-1/2), and acute MI (C92-307 [HERO-1] and C91-018). The studies had a total of 4,965 patients. Eighty-six percent of the patients in this analysis were from Studies C92-304-1 and 2. Results of this meta-analysis are summarized in the following table.

Meta-analysis: Benefit of Bivalirudin versus Heparin in "Ischemic Heart Disease"

	About 7 Days		up to 4-6 Weeks	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Death	0.94 (0.47-1.47)	0.86	0.92 (0.50-1.70)	0.08
MI	0.71 (0.49-1.03)	0.07	0.73 (0.55-0.97)	0.035
Death or Non-fatal MI	0.75 (0.54-1.05)	0.09	0.73 (0.57-0.95)	0.020

reviewer's table

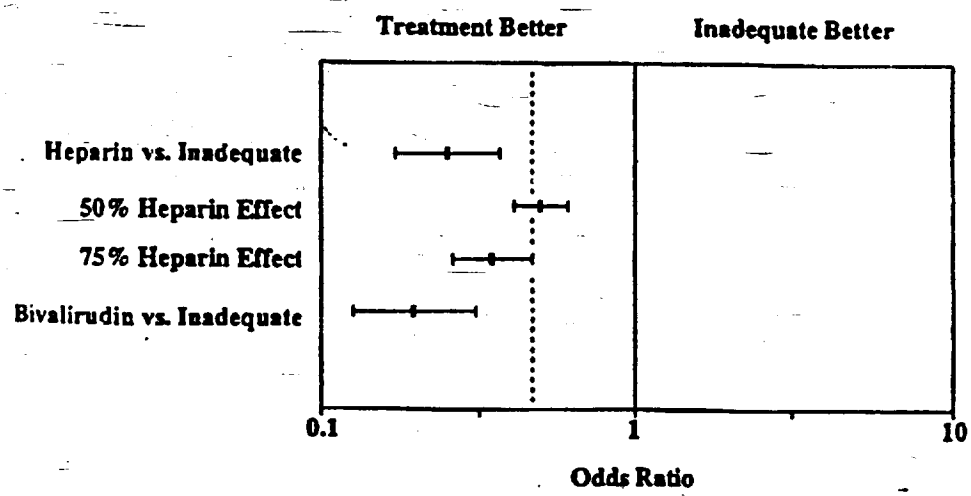
The 133 patients in TIMI-8 were suffering from unstable angina or non-Q wave MI. (This study was discontinued prematurely for business reasons. The 412 patients in HERO-1 had suspected acute MI and death rates at 30 days were 5.1% for bivalirudin group and 6.4% for heparin group. In C91-018 the 116 patients enrolled had experienced acute MI and received [redacted] in addition to study drug; death rates for patients in this study were 4.6% for the bivalirudin group and 6.9% for the heparin group. Also, it should be noted that bivalirudin doses and durations of treatment were differed among these studies.

Reviewer's comments regarding assertion that "bivalirudin is at least as clinically effective as heparin in PTCA": The sponsor has presented new analyses and pooled analyses using a revised definition of MI, a revised definition of the primary composite endpoint, and a revised time at which the primary endpoint is assessed. Though the revisions are not unreasonable, they are all post hoc and all favor the test drug. While the treatment groups generally were well-balanced at study entry and received study drug for comparable amounts of time, it should be recognized that for the duration of hospitalization after completion of study drug administration (generally, after about 18 hrs) management of the individual patients (including post-treatment heparin, which was given in about 25% of all patients) was not standardized but was undoubtedly influenced by clinical assessments of the patients. Mean duration of hospitalization was about 5 days (median, 4 days). Thus, for the majority of the evaluation period in both the protocol-specified analyses ("during hospitalization") and the new analyses presented in the current submission (5 days, 6 days, 8 days, 9 days), a number of non-random factors may have influenced any given patient's course. This effectively confounds the efficacy analysis to an extent that it is not possible to with any degree of accuracy determine the effect of the bivalirudin treatment as compared to the study heparin treatment on the outcome of the PTCA procedure.

The efficacy result is confounded particularly by the fact that some heparin was used during the hospitalization in the majority of patients before and/or after the period of protocol-specified drug administration. Because prior and/or post study use of heparin was not randomly assigned to patients, it is not possible to tease out the effect of non-study heparin, study drug treatment and/or severity of the underlying disease or other factors on the procedure failure rates.

The sponsor rightly points out that there have been changes in the practice of medicine which likely have affected the frequency of some adverse occurrences. These include use of new medicines, such as platelet glycoprotein IIb/IIIa inhibitors (e.g., abciximab) and low molecular weight heparins (e.g., enoxaparin) in PTCA. Though AVC may not be as prevalent now as during the early days of PTCA, it remains a serious event which even when successfully resolved may portend a poorer long-term outcome for patients who suffer AVC. Studies C92-304-1 and C92-304-2 do not tell us anything about how bivalirudin will perform when used in the current clinical milieu. The most appropriate analyses of these studies are the protocol specified ones. Additional investigation of bivalirudin used along with other agents is needed to define the performance of bivalirudin when used in the current clinical practice setting.

3. Bivalirudin is superior to an imputed placebo: Based on the meta-analysis of Study C92-041 and TIMI-7 the sponsor calculates for the endpoint of in-hospital death, MI, and revascularization, an odds ratio for heparin versus imputed placebo of 0.25 (95% CI, 0.017 to 0.37) and an odds ratio for bivalirudin versus heparin of 0.78 (95% CI, 0.62 to 0.99) using the revised composite endpoint (death, MI or revascularization) and the revised MI definition and pooling the pivotal studies (C92-304-1 and C92-304-2). Assuming independence of the pivotal studies and the meta-analysis, the odds ratio for bivalirudin versus imputed placebo is calculated as 0.25 x 0.78 = 0.197 (95% CI, 0.13 to 0.31). The sponsor computes the variance of the imputed result (bivalirudin versus imputed placebo) as equal to the sum of the variances of the meta-analysis and the pooled trials. The sponsor calculates that bivalirudin in the pivotal studies preserved at least 75% of the benefit of heparin anticoagulation. The results of the sponsor's analysis is displayed below:



sponsor's figure, NDA Vol. 15.1, p. 27

Reviewer's comments: As was discussed above, the procedure for imputing the placebo is not valid other than for hypothesis generation. Therefore, the sponsor's calculation of an odds ratio for bivalirudin versus placebo is not valid other than for hypothesis generation. Similarly, the sponsor's comparison of heparin versus placebo is flawed.

The sponsor has not imputed a placebo rate for procedure failure. Rather the sponsor has derived an odds ratio for adequate versus inadequate anticoagulation based on ACT levels in the Narins, Ferguson, and McGarry studies. *This assumes an established causative relationship between ACT level and procedure failure.*

Combination of Efficacy and Safety Analyses:
The sponsor has included in these submissions an additional set of analyses in which the results of the efficacy assessments (death, MI, revascularization) are combined with the main safety assessment (major hemorrhage). Results of this new analysis are summarized in the following table:

Combination of Efficacy and Safety Results

	Number patients with Endpoint (%)		p-value*	odds ratio (95%CI)
	bivalirudin	heparin		
Revised procedural failure (%)[a] or Major Hemorrhage[b]:				
Study C92-304-1	98/1071 (9.1%)	166/1060 (15.6%)	<0.001	0.52 (0.40-0.68)
Study C92-304-2	82/1090 (7.5%)	146/1091 (13.3%)	<0.001	0.53 (0.40-0.70)
Meta-analysis C92-304-1/2	180/2161 (8.3%)	312/2151 (14.5%)	<0.001	0.53 (0.43-0.64)
Major Hemorrhage[b]				
Study C92-304-1	45/1071 (4.2%)	113/1060 (10.7%)	ND	0.34 (0.24-0.49)
Study C92-304-2	31/1090 (2.8%)	86/1091 (7.9%)	ND	0.34 (0.22-0.52)
Meta-analysis C92-304-1/2	76/2161 (3.5%)	199/2151 (9.3%)	ND	0.34 (0.26-0.45)

[a] revised procedural failure = death, MI (revised definition) and revascularization up to 7 days (or end of hospitalization)
[b] major hemorrhage = any of the following: clinically overt bleeding with a fall in Hb level of $\geq$3g/dl; transfusion of $\geq$2 units of blood; retroperitoneal bleeding; intracranial bleeding
* exact test

from sponsor's table, NDA Vol. 20.5, response to Statistical question #2 and Vol. 15.2, pp.283 through 285

Finally, the sponsor estimates the impact of bivalirudin on clinical practice of PTCA for unstable angina as shown below:

Table 19. Estimated impact of bivalirudin on clinical practice of PTCA for unstable angina

CLINICAL OUTCOME	HEPARIN INCIDENCE RATE PER 1000 TREATED	ODDS RATIO BIVALIRUDIN: HEPARIN (95% CI)		ESTIMATED CHANGE IN NUMBER OF EVENTS		
				LL	MID	UL
Death, MI or revascularization	79	0.78	(0.62-0.99)	-30	-17	-1
Major Hemorrhage	93	0.34	(0.26-0.45)	-69	-60	-51
Death, MI, revascularization or major hemorrhage	145	0.53	(0.43-0.64)	-83	-68	-52

sponsor's table, NDA Vol. 15.1, p. 41

Reviewer's comments: In these new analyses the significant results in favor of bivalirudin are driven mainly by inclusion of "major hemorrhage" in the redefined efficacy endpoint.

There is no question that in Studies C92-304-1 and C92-304-2 significantly fewer bivalirudin patients than heparin patients had any bleeding complication and significantly fewer bivalirudin patients than heparin patients had major hemorrhage. What is not clear is whether the bleeding rates observed in these studies reflect rates that would have been observed using currently recommended less aggressive heparin regimens and with monitoring of aPTT during treatment with heparin. Though the bleeding rates in these studies were in the same ballpark as published rates for bleeding complications in PTCA, to extrapolate that information across studies requires a leap of faith.

A table showing the sponsor's summary of published hemorrhage rates in PTCA studies is shown below. In most of these studies GPIIb/IIIa inhibitors were used in combination with heparin during PTCA and for 24 hrs after the procedure.

Table 18. Cleveland Clinic Meta-Analysis[1]: Hemorrhage Rates Using TIMI Criteria in 6 Reference Trials And Pivotal Trials

STUDY (REFERENCE)	PATIENTS EVALUABLE FOR MAJOR HEMORRHAGE EVENTS	ALL CAUSE HEMORRHAGE RATES (95% CI) (TIMI CRITERIA)			
		MAJOR HEMORRHAGE		MINOR HEMORRHAGE	
CAPTURE	635	3.5%	(2.0, 4.9)	2.0%	(0.9, 3.1)
EPIC	675	6.5%	(4.7, 8.4)	10.1%	(7.8, 12.3)
EPILOG	898	3.2%	(2.1, 4.4)	3.9%	(2.6, 5.2)
EPILOG-STENT	809	2.2%	(1.2, 3.2)	1.7%	(0.8, 2.6)
IMPACT-II	1257	4.8%	(3.6, 6.0)	9.5%	(7.9, 11.2)
RAPPORT	181	7.7%	(3.8, 1.2)	21.5%	(15.6, 27.5)
All Published Trials	4,455	4.2%		6.5%	
304-1/2 heparin	2,151	2.9%	(2.2, 3.6)	7.6%	(6.5, 8.7)
304-1/2 bivalirudin	2,161	1.1%	(.07, 1.5)	3.2%	(2.5, 3.9)

[1] The full analysis is provided in Appendix VI, and source materials referenced

sponsor's table, NDA Vol. 15.1, p. 39

Note that while the rate of major hemorrhage for the heparin group in Studies C92-304-1/2 was 9.3% of patients using the protocol specified definition of major hemorrhage [any intracranial or retroperitoneal hemorrhage or overt bleeding associated with a decrease in hemoglobin level of $\geq$3 g/dl or leading to a transfusion of $\geq$2 units of blood], the major hemorrhage rates for heparin and bivalirudin included in the above table are based on the TIMI definition, namely, bleeding that was "intracranial or associated with a decrease in hemoglobin >5g/dl (or 15% in hematocrit)". In a Dutch study of heparin versus heparin + hirudin where a broader definition of major bleeding was used, similar rates of major bleeding were reported (4.7%-7.4%) (Serruys et al NEJM, 333:757 (1995)). Bleeding rates are probably significantly influenced by operator and site.

Additional Information:
Annual Report: The most recent annual report for bivalirudin ——— was submitted to the IND on 1/29/99 (N-200 YY)(IND Vol. 44.1) and covered the period 12/23/97-11/2/98. The NDA for bivaliruding had been submitted in December, 1997 and no clinical trials were underway during the period covered. The annual report outlined the further plan for clinical studies of bivalirudin to include the following:

- *The Effect of Hirulog in Combination with ReoPro on Laboratory Coagulation Parameters and Incidence of Clinically Significant Bleeding in Patient Undergoing PTCA (TMC-97-01)*[original protocol submitted 11/4/97; N-163]: This study is designed to compare effect of ReoPro + bivalirudin versus ReoPro + low-dose heparin on laboratory coagulation parameters and incidence of clinically significant bleeding during hospitalization in about 30 patients in two centers. Parameters to be assessed include ACT levels, thrombin and platelet inhibition, and safety endpoints (i.e., incidence of death and hemorrhagic stroke; incidence of major bleeding or red blood cell transfusion; incidence of adverse experiences). ReoPro + bivalirudin patients will receive a bolus of 0.25mg/kg abciximab and a bolus of 1mg/kg bivalirudin 10-60 min before crossing the lesion, followed by a 0.125ug/kg/min infusion of abciximab (to a maximum of 10 ug/min) for 12 hrs and a 2.5mg/kg/hr infusion of bivalirudin for 4 hrs. Patients randomized to ReoPro + low dose heparin will receive a bolus of 0.25mg/kg of abciximab 10-60min before crossing the lesion, followed by a 0.125ug/kg/min infusion of abciximab for 12 hrs. They will also receive low-dose weight adjusted heparin to achieve an activated clotting time (ACT) of about 200 seconds prior to the start of the procedure. All patients will receive aspirin before and after the procedure.
  [Reviewer's Note: According to the Safety Update submitted by the sponsor 8/5/99 and discussed below, this study has been completed. The study is described and submitted results are discussed below].

- *A Multicenter, Open-Label, Randomized Trial Comparing Clinical Outcome with Hirulog and Provisional Abciximab versus Planned Abciximab and Low-dose Heparin in Patients Undergoing Percutaneous Intervention (TMC-97-02)* [original protocol submitted 1/27/98; N-167]: This study is designed to compare the safety and effectiveness of two treatment strategies: low-dose weight adjusted heparin combined with abciximab (ReoPro) versus bivalirudin combined with abciximab. This is planned as a Phase III multicenter, randomized trial in about 5000 patients at 100-150 centers. Patients randomized to bivalirudin will receive a 1mg/kg bolus just prior to starting the procedure followed by a 2.5mg/kg/hr infusion for 4 hrs. Patients randomized to abciximab will receive a bolus of 0.25mg/kg 10-60 minutes before crossing the lesion, followed by a 0.125ug/kg/minute infusion of abciximab (to a maximum of 10ug/min) for 12 hrs. All patients will receive aspirin before and daily for 6 months after the procedure. The sponsor aims to demonstrate equivalence of the two treatment arms with respect to incidence of death, myocardial infarction and/or urgent revascularization within 30 days of randomization.

- *The Effect of Hirulog in Combination with Integrelin on Laboratory Coagulation Parameters and the Incidence of Clinically Significant Bleeding in Patients Undergoing Percutaneous Coronary*

Intervention. This study protocol has not yet been submitted to the IND. The study will randomize 30 patients in 2:1 ratio to either bivalirudin 1mg/kg bolus followed by 2.5mg/kg/hr infusion x 4 hrs plus Integrilin 180ug/kg bolus and 2ug/kg/hr infusion for 20-24 hrs or Integrilin (as above) plus low-dose weight-adjusted heparin to maintain a target ACT of 300-350 seconds. All patients will receive aspirin. Patients will be followed during hospitalization for thrombin levels and platelet inhibition and incidence of death hemorrhagic stroke, major bleeding, RBC transfusion and incidence of death, myocardial infarction and/or urgent revascularization will be assessed until discharge or 7 days post-randomization, whichever comes first.

- *The Effect of Bivalirudin in Combination with Ticlopidine on Laboratory Coagulation Parameters and the Incidence of Clinically Significant Bleeding in Patients Undergoing Percutaneous Intervention and Stenting* [original protocol submitted 1/19/99; N-198]. The study will randomize 30 patients (3 centers) in 1:1 ratio to either bivalirudin 1mg/kg bolus followed by 2.5mg/kg/hr infusion x 4 hrs plus ticlopidine 250mg BID for 48-72 hrs or low-dose weight-adjusted heparin to maintain a target ACT of 300-350 seconds plus ticlopidine (as above). All patients will receive aspirin. Patients will be followed during hospitalization for thrombin activity and platelet inhibition and adverse events (including major hemorrhage, RBC transfusion, death, etc.). Incidence of death, myocardial infarction and/or urgent revascularization will be assessed until discharge or 14 days post-randomization, whichever comes first.

- *The Hirulog Early Reperfusion/Occlusion Trial (HERO-2)* [original protocol submitted 6/13/97; N-154]: This trial is designed to be an open-label, randomized comparison of bivalirudin versus heparin in 17,000 patients receiving aspirin and [redacted] for treatment of acute myocardial infarction. Patients presenting with MI will be randomized in 1:1 ratio to either bivalirudin (0.25mg/kg bolus followed by 0.5mg/kg/hr infusion x 12 hrs the 0.25mg/kg/hr x36-48 hrs) plus [redacted] (1.5MU IV over 30-60 minutes) or heparin (5,000IU bolus followed by continuous infusion (weight-adjusted) for 48-60 hrs to keep aPTT at 50-75 seconds. Primary objective is to show lower rate of mortality at 30 days in the bivalirudin + [redacted] group. Rates of in hospital reinfarction and death at 30 days , incidience of non-fatal stroke, intracranial hemorrhage, bleeding events and other safety parameters will be assessed.

- *An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS) in Patients Undergoing Percutaneous Coronary Intervention (PCI)* [original protocol submitted 12/23/98; N-196]: This is a multicenter, open-label, study in which patients who have new or previous HIT/HITTS and who require anticoagulation for PCI will receive bivalirudin 1mg/kg bolus followed by 2.5mg/kg/hr infusion x 4 hrs. If continued anticoagulation is needed after the procedure, patients bivalirudin dose will be decreased to 0.2mg/kg/hr for up to 20 hrs. It is estimated that at least 50 patients will be treated with bivalirudin at about 20 centers. The aim of the study is to assess major bleeding events during or within 48 hrs after stopping bivalirudin treatment (or at hospital discharge). ACTs, platelet counts and aPTTs will be followed during hospitalization. All patients will receive aspirin.

- *The Influence of Dose and Kidney Function on Bivalirudin Pharmacokinetics and Pharmacodynamics in Patients Undergoing Percutaneous Coronary Artery Angioplasty (PTCA)* [original protocol submitted 12/2/98; N-188]: This is to be a PK/PD study in 30 patients aged 18-85 years with varying degrees of renal impairment who are undergoing PTCA. The study will be done at two sites (New Zealand and Australia). The aims are to determine bivalirudin clearance in these patients at the dose being proposed in the NDA submission (1mg/kg IV

bolus followed by 2.5mg/kg/hr infusion x 4 hrs, followed by 0.5mg/kg/hr infusion), to determine if the clearance is dose dependent and/or dependent on renal function and to assess the proportion of unchanged drug renally cleared. All patients will receive aspirin. ACTs will be monitored and patients will be followed for bleeding and ischemic complications.

Safety Update: The sponsor has submitted a Safety Update for bivalirudin (submission dated 8/5/99, NDA Vols. 20.6 through 20.11). The safety update includes study information up to May 28, 1999. It contains interim reports for four clinical trials in PTCA (see below) and the final report for TMC-9701A (CACHET Pilot Study A). Study TMC-9701A is discussed below and information about the ongoing studies is summarized in a table below.

Study TMC-9701A: *(CACHET Pilot Study A) The Effect of Hirulog in Combination with ReoPro on Laboratory Coagulation Parameters and Incidence of Clinically Significant Bleeding in Patient Undergoing PTCA* [carried out 12/2/98 through 2/2/99

(Note: The sponsor's final report was submitted for this study; however, the supplemental tables and analyses (Section 13) are not included in the submission).

In this study a total of 60 patients were randomized to either:

- bivalirudin 1.0mg/kg intravenous bolus followed by 2.5mg/kg/hr infusion x 4 hrs and ReoPro 0.25mg/kg intravenous bolus followed by 0.125ug/kg/min infusion (to a maximum of 10ug/min) for 12 hrs. (The bivalirudin bolus and initiation of infusion preceded the ReoPro bolus and infusion), or
- low-dose weight adjusted heparin for the duration of the procedure (target ACT 200-300 sec) and ReoPro 0.25mg/kg intravenous bolus followed by 0.125ug/kg/min infusion (to a maximum of 10ug/min) for 12 hrs. (The initial heparin bolus preceded the ReoPro bolus and infusion. Additional heparin boluses were given every 30 min as needed to maintain ACT between 200-300 secs, or a 7U/kg/hr continuous infusion of heparin was begun).

Mean age of patients was 59 years and 87% of patients were males. All patients received the treatment regimen to which they were randomized; however, 8 patients (6 Hirulog/ReoPro and 2 heparin/ReoPro) did not receive the full study drug dose. The treatment groups were somewhat unbalanced with regard to location of disease (left circumflex disease in 33.3% of Hirulog/ReoPro patients and 16.7% of heparin/ReoPro patients) and number of vessels involved (23.3% of Hirulog/ReoPro patients and 3.6% of heparin/ReoPro patients with multivessel disease). All patients underwent the procedure and the type of intervention was similar in the two treatment groups (about 90% had stents placed). Eight patients (6 bivalirudin/ReoPro and 2 heparin/ReoPro) had study medication stopped prematurely. The sponsor lists two Hirulog/ReoPro patients as having study medication discontinued because of bleeding complications (hematoma, gross hematuria and thrombocytopenia in a 69 yr old man; and oozing blood at femoral artery puncture site, femoral bruit, eccymosis, hematoma, groin pain and back pain in a 46 yr old man); and two heparin/ReoPro patients as having study medication discontinued because of bleeding complications (right coronary artery perforation in a 52 yr old man and hypotension and hematoma in a 68 yr old woman). Reasons for study drug discontinuation in the other 4 Hirulog patients are not provided. Though treatment groups were similar with regard to baseline ACT values (132 sec Hirulog/ReoPro; 129.5 sec heparin/ReoPro), after study drug administration, the ACT for the two groups differed significantly as shown in the sponsor's table below:

Text Table 6. Median ACT Values-Safety Patient Population

ACT PARAMETER	[illegible]	REOPRO/HEPARIN	P-Value
Baseline ACT	132 (n=29)	129.5 (n=30)	0.505 NP
30 Minute ACT	375 (n=28)	265.5 (n=28)	<0.001 NP
60 Minute ACT	351 (n=26)	239.5 (n=22)	<0.001
90 Minute ACT	371.5 (n=24)	230 (n=26)	<0.001
120 Minute ACT	350 (n=26)	189 (n=27)	<0.001
150 Minute ACT	347 (n=27)	163 (n=27)	<0.001
180 Minute ACT	335.5 (n=26)	148 (n=27)	<0.001 NP
210 Minute ACT	335.5 (n=28)	131 (n=27)	<0.001 NP
240 Minute ACT	300 (n=27)	125 (n=19)	<0.001 NP

(NP)=Nonparametric Test.
Data source: Section 13, Tables 8.17.1, 8.17.1A, 8.17.1B, 8.18.1

sponsor's table, NDA Vol. 20.7, p. 50

In addition, statistically significant between-group differences were noted for the parameters of ADP-induced platelet aggregation, rapid platelet function assay (RPFA), F1.2 (thrombin formation), and ß-thromboglobulin (ß-TG) for platelet activation at one or more time points, as shown in the sponsor's table below:

Text Table 7. Median Hemostasis Results: Statistically Significant Treatment Differences (Safety Patient Population)

HEMOSTASIS PARAMETER (UNITS)/TIMEPOINTS		[illegible]	REOPRO/HEPARIN	P-VALUE†
ADP (% aggregation)				
Baseline:	ADP 5 µM	55.00	48.50	0.791
	ADP 20 µM	62.00	68.00	0.356 NP
4 hr:	ADP 5 µM	2.00	0.00	0.084 NP
	ADP 20 µM	5.00	3.00	0.053 NP
% change at 4 hr:				
	ADP 5 µM	94.92	100.00	0.043 NP
	ADP 20 µM	90.77	95.08	0.026 NP
RPFA (% aggregation, slope)				
Baseline slope		388.93	390.04	0.861
1 hr % aggregation		8.00	4.50	0.048 NP
change in % aggregation		92.00	95.50	0.048 NP
1 hr slope		20.10	9.59	0.288 NP
Thrombin formation/F1.2 (nM)				
Baseline		1.44	1.11	0.038
4 hr		1.08	1.05	0.334 NP
4 hr/baseline ratio		0.62	0.83	0.005 NP
24 hr		1.19	1.61	0.024 NP
24 hr/baseline ratio		0.82	1.38	<0.001 NP
Platelet activity/ß-TG (IU/ml)				
Baseline		147.90	123.94	0.072 NP
4 hr		96.35	114.54	0.696 NP
4 hr/baseline ratio		0.64	0.89	0.045 NP

† NP = Nonparametric Test
Data source: Section 13, Tables 14.0.1-14.3.1, 15.0.1-15.3.1, and 17.0.1-17.3.1

sponsor's table, NDA Vol. 20.7, p. 53

Only one patient (Hirulog/ReoPro group) suffered a major hemorrhage. Major and/or minor bleeding occurred in 7 (23.3%) Hirulog/ReoPro patients and in 5 (16.7%) heparin/ReoPro patients.

Six Hirulog/ReoPro patients and 4 heparin/ReoPro patients had decrease of serum hemoglobin of ≥2.00mg/dl but no patients had transfusion. There were no deaths, strokes (hemorrhagic or non-hemorrhagic), or revascularizations (urgent or non-urgent) during the study. One heparin/ReoPro patient suffered a myocardial infarction after PTCA. Median length of hospital stay was 1 day (range, 8 hrs- 10 days) and was similar in the two treatment groups.

> *Reviewer's comments:* This study does not contribute significantly to the application. The protocol stipulated that safety variables would be assessed "within 7 days of randomization or until hospital discharge, whichever occurred first"; however, because most patients were discharged within the first 24-48 hrs, the followup for safety reflected in this report is very limited. Very few events occurred in either treatment group during the followup time. It may be useful to know what event rates (death, MI, revascularization) were at 30 days, however, because of the small size of the study even those numbers are likely to be difficult to interpret.

Results of interim analysis of 4 other studies of bivalirudin in PTCA that are ongoing are summarized in the table below

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