CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-873

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

NDA #: 20-873

Drug: Angiomax (bivalirudin) Injection

Drug Class: 1S

Indication: Anticoagulant for patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for the treatment of unstable angina.

Sponsor: The Medicines Company

Clinical Reviewer: Kathy Robie-Suh, M.D., Ph.D., HFD-180

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Date submitted: November 11, 1999; December 20, 1999; January 7, 2000

Date Received: November 12, 1999; December 21, 1999

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a potentially life-saving procedure in patients with unstable angina. According to documentation provided by the sponsor, published data and extensive clinical experience have established heparin as an effective anticoagulant which is used to prevent clot formation following PTCA. Although the effectiveness of heparin has long been noted, it is not approved for PTCA for the treatment of unstable angina.

2. Cycle-1

An NDA was submitted on December 1997 to demonstrate the safety and efficacy of bivalirudin versus heparin in patients undergoing PTCA for the treatment of unstable angina. The sponsor's intent was to show superiority of bivalirudin over heparin during PTCA for the treatment of unstable angina. Although not specifically labeled for PTCA, the sponsor claims that heparin is used extensively as an anticoagulant in a variety of interventional settings, including arterial and cardiac surgery, and has been routinely administered during PTCA since the first procedure was performed in 1970s. However, no prospective, placebo-controlled trials were submitted to support the effectiveness of heparin as an anti-coagulant during PTCA for the treatment of unstable angina (the medical division is unaware of any such studies).

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 endpoint "procedural failure." Following a request by the sponsor, a meeting was held on January 15, 1999 to discuss the deficiencies of the trials. It was recommended that the applicant consider:

(1) estimating the treatment effect of heparin relative to placebo in PTCA based upon historical data,

(2) demonstrate that the clinical effects of bivalirudin exceed the effect established in (1).

3. 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 of clinical effects of bivalirudin (including an estimation of the clinical effects of bivalirudin and heparin in PTCA compared to "Imputed Placebo" based on three papers).

Conclusions

1. The information provided in this resubmission has not contributed to our understanding (statistically) of the effects of heparin when used with PTCA.

2. The applicant has not established that bivalirudin is significantly better than heparin for the revised definition of the primary endpoint (dropping AVC, revised definition of MI, and reduction the hospitalization period to 7-day or earlier). Further, these modifications of the primary endpoint and combining two studies after looking at the data are not acceptable from a statistical point of view.

3. The studies submitted indicate, based on upper bounds of the confidence intervals in Table 1.3, that bivalirudin is no more than 1-2% less effective than heparin (approximately 10-25% relative). However, the two pivotal studies were not designed as non-inferiority or equivalence trials. Therefore, an equivalence/noninferiority margin was not specified in the protocol. In addition, heparin (active control in this submission) is not approved for use in PTCA. Further, the protocols allowed patients in both study arms to receive heparin after discontinuation of study treatment. For these reasons, the sponsor has been unable to establish statistically (i.e., what margin to exclude) that the confidence intervals presented support the efficacy of bivalirudin.

An approvable letter was sent on 10/28/99 for the application identifying a number of Clinical, CMC, and Biopharmaceutical deficiencies. 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 bivalirudin compared to heparin, as

conventionally used and monitored. Either superiority trial or non-inferiority /equivalence trial would be acceptable.

4.0 Cycle-3

The sponsor responded to the approvable letter on 11/11/99. The indication being sought has been changed to "Bivalirudin is indicated as an anticoagulant for undergoing PTCA for unstable angina presenting within two weeks of myocardial infarction." The sponsor does not propose any new efficacy study.

The statistical review (page 29, dated October 2, 1997) stated the following recommendation for the Post-MI subgroup:

"The protocol stated objective for this study (superiority of bivalirudin over heparin) was not achieved. Efficacy is suggested for the post-MI subgroup of patients (19% of the enrolled patient population). But this would need to be confirmed in another Phase III study. Therefore, this reviewer's recommendation is for another study to support the superiority in post-MI patients."

The statistical review (page 28, dated October 2, 1997) stated the following concerns for the post-MI subgroup:

"For the post-MI sub-population, the incident of procedural failure was significantly lower in the Hirulog group than in the heparin group in study C92-304-2. A numerical trend from Hirulog over heparin was indicated in study C92-304-1. However, it should be noted that the analysis of post-MI sub-group patients was not prospectively specified in the protocol."

The recommendations listed above have not been affected by the most recent submission.

/S/

M. Mushfiqur Rashid. Ph.D.
Mathematical Statistician

3/15/00

Concur:
Dr. Flyer

3/15/00

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STATISTICAL REVIEW AND EVALUATION

NDA #: 20-873

Drug: Angiomax (bivalirudin) Injection

OCT 13 1999

Drug Class: 1S

Indication: Anticoagulant for patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for the treatment of unstable angina.

Sponsor: The Medicines Company

Clinical Reviewer: Kathy Robie-Suh, M.D., Ph.D., HFD-180

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Documents Reviewed: Volumes: 17.1-17.5; dated April 28, 1999.

User Fee Due Date: October 28, 1999.

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a potentially life-saving procedure in patients with unstable angina. According to documentation provided by the sponsor, published data and extensive clinical experience have established heparin as an effective anticoagulant which is used to prevent clot formation following PTCA. Although the effectiveness of heparin has long been noted, it is not approved for PTCA for the treatment of unstable angina.

An NDA was submitted on December 1997 to demonstrate the safety and efficacy of bivalirudin versus heparin in patients undergoing PTCA for the treatment of unstable angina. The sponsor's intent was to show superiority of bivalirudin over heparin during PTCA for the treatment of unstable angina. Although not specifically labeled for PTCA, the sponsor claims that heparin is used extensively as an anticoagulant in a variety of interventional settings, including arterial and cardiac surgery, and has been routinely administered during PTCA since the first procedure was performed in 1970s. However, no prospective, placebo-controlled trials were submitted to support the effectiveness of heparin as an anti-coagulant during PTCA for the treatment of unstable angina (the medical division is unaware of any such studies).

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 endpoint "procedural failure." Following a request by the sponsor, a

meeting was held on January 15, 1999 to discuss the deficiencies of the trials. It was recommended that the applicant consider:

(1) estimating the treatment effect of heparin relative to placebo in PTCA based upon historical data,

(2) demonstrate that the clinical effects of bivalirudin exceed the effect established in (1).

The rest of this review is organized as follows: Section 2 summarizes the original review of this submission, Section 3 summarizes the comparison of heparin with imputed placebo, Section 4 contains revised analyses from the original submission, and Section 4 summarizes conclusions and recommendations.

2. Summary of Previous Statistical Review

There are two Phase III studies in this submission. Both studies C92-304-1 and C92-304-2 are multi-center, double blind, randomized clinical trials. Subjects were stratified by post-MI versus otherwise. The purpose of each study is to compare the safety and efficacy of bivaluridin versus heparin in patients with unstable angina undergoing PTCA. As was noted previously, heparin is not approved for this indication.

Study Endpoints:

In both studies, the primary efficacy endpoint was the composite endpoint "procedural failure" defined as the occurrence of any one of the following:

1) Death, occurring during hospitalization;
2) Documented myocardial infarction (MI) not present on enrollment, occurring during hospitalization;

MI was confirmed if at least 2 of the following 3 criteria were present:

a) prolonged angina (>30 minutes)
b) total creatine phosphokinase (CK or CPK) elevation greater or equal to 2 times the upper limit of normal and CK-MB greater than 4%
c) new development of 2-step Minnesota q-wave codes or new left bundles branch block (not rate-related)

3) Clinical deterioration of cardiac origin in a patient's status during hospitalization requiring revascularization (angioplasty or coronary artery bypass graft (CABG)) or placement of an aortic counterpulsion balloon; and
4) Angiographic evidence of decreased coronary blood flow in the form of either established or impending abrupt vessel closure (AVC).

Secondary efficacy endpoints were:

1) the individual components of procedural failure;
2) the procedural failure in a patient who received continuous infusions of heparin within 1 hour prior to study drug administration and
3) the occurrence of clinical events (death, MI, symptom-necessitated coronary angiography, symptom necessitated revascularization PTCA/CABG, ischemic pain requiring re-hospitalization and evidence of restenosis).

Sample Size Estimation/Randomization Schemes and Study Conduct:

In both studies, sample of sizes of 2000 evaluable patients were planned in order to detect, with at least 80% power, and a type I error rate (two-sided) of 5%, a 33% reduction in the event rate for bivalirudin relative to heparin. Note that the sample size estimation procedure (two-sample test for equality of proportions) did not incorporate covariates used in the primary analysis of efficacy data.

The following table shows the patient disposition for studies C92-304-1 and C92-304-2.

Table 1.2 (reviewer's Table): Patient Disposition

Population	# of Centers	Drug Group (# randomized)	Treated Sample Size(%)		
			Post-MI	Non-Post MI	Total
C92-304-1	73	heparin (1168)	203 (19%)	857 (81%)	1060
		bivalirudin (1150)	206 (19%)	865 (81%)	1071
C92-304-2	45	heparin (1172)	169 (16%)	922 (84%)	1090
		bivalirudin (1182)	163 (15%)	927 (85%)	1091

Safety:

In both studies, the stated primary safety endpoint was clinically significant bleeding which is a known consequence of heparin. All bleeding events were classified by the investigator as major or minor. Bleeding was classified as major if it was 1) intracranial, 2) retroperitoneal, 3) clinically overt leading to transfusion of 2 or more units of blood.

Other safety measurements included monitoring of adverse events, pre- and post-treatment clinical laboratory evaluations, and monitoring of vital signs.

2.1 Analysis of Rates Based on the Primary Endpoint:

Efficacy:

As specified in the protocol, the sponsor assessed the treatment group differences in the incidence of procedural failure using the likelihood ratio test from logistic regression. According to the protocol, the model (main effects) was adjusted for the following covariates: site, post-MI group, age (<65, greater or equal to 65), multi-vessel disease, pre-procedural percent stenosis, and treatment. Odds ratios (bivalirudin/heparin) of procedural failure and 95% confidence intervals (CI) were obtained from the logistic regression model. The sponsor's statistical analysis of the efficacy data for evaluable patients was similar to the analyses of the ITT population. This reviewer performed both adjusted (based on logistic regression using the covariates: treatment, pooled site. age category, multivessel disease, percent stenosis) and unadjusted (without adjusting for these covariates) analyses for assessing the treatment group differences. This reviewer's analysis results are in agreement with the analysis results provided by the sponsor for the ITT population.

ITT Population:

Table 1.3 (reviewer's): Incidence of Procedural Failure During Hospitalization - ITT Population

Study #	Proportion of Patients With Procedural Failure (%)		Confidence Interval*: Difference in percenatge (bivalirudin-heparin)		p-value		Odds ratio (95% CI)	
	bivalirudin	heparin	95%	99.9%	Adj	Unadj**	Adjusted	Unadjusted
C92-304-1	77 /1071 (7.2%)	90/1060 (8.5%)	-1.3% (-3.6%, 1%)		.253	.295	.835 (.608,1.16)	. 831 (.604,1.142)
C92-304-2	83/1090 (7.6%)	87/1091 (8.0%)	-.4% (-2.7%, 1.9%)		.796	.811	.951 (.695,1.301)	.959 (.700,1.314)
C92-304-1/2	160/2161 (7.4%)	177/2151 (8.2%)	-.8% (-2.4%,.8%)	-.8% (-2.9%,1.3%)	.313	.335		.89 (.71. 1.11)

* Normal approximation to binomial; **Fisher's exact;

From the above table it is seen from both adjusted and unadjusted analyses that the incidence of procedural failure during hospitalization in both studies C92-304-1 and C92-304-2 for the bivalirudin group was not statistically significantly different from the heparin treatment group. Thus the superiority claim being sought by the sponsor was not supported by the primary analysis results.

The individual trial confidence interval (95%) allow for a difference relative to control

of 1.0% and 1.8% (absolute). The pooled results allow for a difference of .8% (95% CI) and 1.3% (99.9% CI). The latter interval reflects a more stringent "single trial" approach.

Safety Analyses

This reviewer compared the occurrence of bleeding events by the likelihood ratio test (based on a logistic regression model (main effects) with covariates for treatment, site, post-MI group, age (<65, greater or equal to 65), multi-vessel disease, and pre-procedural percent stenosis) and the Fisher's exact test (not adjusted for covariates). This reviewer's analysis results are consistent with the analysis results provided by the sponsor.

Both the incidence of major bleeding and the time to first occurrence of major bleeding significantly favored bivalirudin over heparin in all analysis groups in both studies. In both studies, significant differences in favor of bivalirudin were also seen for "any bleeding."

In the following table we summarize bleeding events according to presence or absence of major bleeding (treatment emergent) and any bleeding (treatment emergent).

Table 1.4 (Reviewer's table): **Incidence of Treatment-Emergent Bleeding (ITT Population)**

Study #	Proportion of Patients With Treatment-Emergent Bleeding (%)				p-value			
	Major		Any		Major Bleeding		Any Bleeding	
	bivalirudin	heparin	bivalirudin	heparin	Adj.	Unadj	Adj	Unadj
C92-304-1	47 /1071 (4%)	113/1060 (11%)	593/1071 (55%)	864/1060 (82%)	.0001	<.0001	.0001	<.0001
C92-304-2	32/1090 (3%)	86 /1091 (8%)	561/1090 (51%)	835/1091 (77%)	.0001	<.0001	.0001	<.0001

3. Comparisons of historical placebo rates

The sponsor provided three studies to establish the clinical effect of heparin relative to placebo for procedural failure as defined for studies C92-304-1 and C92-304-2.

Narins C. R. et al.(1996,93,667-671)

The purpose of this study was to determine whether the degree of heparin anticoagulation during coronary angioplasty, as measured by the activated clotting time, is related to the risk of abrupt vessel closure.

Sixty two cases of in- and out-of laboratory abrupt closure in patients whom intra-procedure activated clotting times were measured were identified from a population of 1290 consecutive patients who underwent non-emergency coronary angioplasty. This group was compared with a matched control population of 124 patients who did not experience abrupt closure.

Hemochron ACTs of 62 patients who experienced ishchemic complications (death, MI. and need for urgent revascularization) after angioplasty (cases) were compared to 124 matched patients (from a different study) without complications (controls). Activated clotting times were measured after the final heparin bolus before the initial balloon inflation. All patients received aspirin. Relative to the control population, patients who experienced adverse clinical outcomes had significantly lower initial ACT (350 vs. 380 seconds, p-value = .004) and minimum (345 vs. 370 seconds, p-value .014) median ACT times. There were 15/62 cases who had initial HemoChron ACT < 300 seconds and 12/124 control patients who had ACT < 300 seconds. The odds ratio for adverse outcomes (i.e., clinical endpoint) was .34 (95%: CI, .15, .77).

Table 3.1: Adequate versus Inadequate Heparin Anticoagulation (case - control studies: Narins et al.)

sample size		proportion (%) of patients with ACT<300		diff (%) (control-case)	p-value (Fisher's)	odds ratio (95% CI)
control	case	control	case			
124	62	12/124 (9.68%)	15/62 (24.19%)	-14.51%	.014	.336 (.146, .771)

Note that the sponsor assumed that the control group had adequate heparin anticoagulation and the case group had inadequate heparin anticoagulation. Although the control group is significantly superior to the case group (placebo group with respect to ACT<300), the results do not quantify the degree of treatment effect for heparin in terms of procedural failures. Rather, the results of this study confirm that ACT < 300 is a prediction of adverse outcomes.

Ferguson J.J. et al. (1994, 23,1061-5)

In a case control study, Ferguson et al. reviewed 1469 consecutive PTCA procedures performed at a single center. HemoTech ACTs of 503 patients with major in-hospital complications (death, emergent or urgent bypass surgery: cases) were compared to 400 randomly selected, matched, uncomplicated patients from the same series (controls). All patients had activated coagulation times (ACT) measures at baseline, after heparin therapy, and at the end of the procedure. There were no differences in baseline ACTs between the two groups. Cases had significantly lower ACTs after heparin therapy and at the end of the procedure. There were 63/103 cases with initial HemoTech ACT<250 seconds, and 108/400 control patients with ACT <250 seconds. The odds ratio was .23 (95% CI: .15 to .37).

Table 3.2: Adequate versus inadequate heparin anticoagulation (case - control studies: Ferguson et al.)

sample size		proportion of patients with ACT<250 (%)		Difference (%)	p-value (Fisher's exact)	odds ratio (95% CI)
control	case	control	case			
103	400	108/400 (27%)	63/103 (61.17%)	-34.17 %	<.0001	.235 (.149 ..370)

Although the control group is significantly superior to the case group (placebo group), the results do not quantify the treatment effect of heparin (i.e., reduction of procedural failure rate due to the use of heparin) for procedural failures. This study shows that patients with complications tend to have lower ACT after treated with heparin than subjects without complications.

McGarry T. F. et al. (1992, 123, 1445)

McGarry et al. analyzed 487 consecutive patients who underwent elective angioplasty at a single center. A total of 336 patients had documented partial thromboplastin times (PTT). Patients were divided into two groups: those with PTT>=3 times the control value (n=271), and those with PTT<3 times the control value (n=65). PTT samples were obtained after the procedure and before discontinuation of heparin for sheath removal. All patients received aspirin. Clinical outcomes included death and ishcemic complications (chest pain with 1 mm ST segment elavation in the dilated territory associated with elevation in creatine kinase MB fraction) prior to hospital discharge. There was a statistically significant reduction in the incidence of ischemic events (1.5% vs. 9.2%, p< .001) in patients with PTT values <3 times the control value. The odds

ratio for adverse outcomes was .22 (95% CI .08 to .65).

Table 3.3: Summary of procedural failure (McGarry et al.)

sample size		proportion (%) of patients with clinical outcomes		diff.(%) (control-case)	p-value Fisher's exact)	odds ratio (95% CI)
PTT < 3x control	control: PTT>=3x control	PTT < 3x control	control: PTT>=3x control			
65	271	7/65 (10.77%)	7/271 (2.58%)	-8.19 %	<.0001	.22 (.074,.651)

It is seen that the "PTT>3 X control group" has a significantly higher event rate. Note that this study is not a case-control study. This reviewer computed a 95% confidence interval for PTT < 3 x control. The interval is [.032, .183]. Because the procedural failure rates (see Table 4.1) for both heparin and bivalirudin C-92-304-1, C-92-304-2 and C-92-304-1/2 fall with in the interval [.032, .183], the failure rates of both bivalirudin and heparin may not be distinguishable from the PTT < 3 x control. Therefore, the rates observed in the two clinical trials contained in the NDA for bivalirudin cannot be said to be different from those expected for inadequate heparinization (i.e., < 3x control). It is to be noted that the sample size (65) is not large enough to draw a firm conclusion.

Adequate Heparinzation Versus Inadequate Heparinazation: A Meta Analysis

Narins et al. and Ferguson et al. may be termed case-control studies. However, McGarry et al is not a case control study. Therefore, a meta analysis of these three studies is not appropriate. Although the sponsor claimed that the three studies are similar, the three studies are not similar with respect to the heparin doses and procedural indications as can be seen from Table 3.4.

Table 3.4: Comparisons of the three studies

	Narins et al.	Ferguson et al.	McGarry et. al.
Total heparin dose (mean+/- s.d.):			
Controls	13,413+/- 4290	17,800 +/- 1900	Not reported
Cases	16,532 +/-7341	13,700 +/- 4800	Not reported
Procedural Indications	Non-emergency	Not reported	"Elective"

It can be seen in Narins et al. the control group received a lower heparin dose (on the

average) than the case group. Also the cases had more heparin than the control in Narins et al. while the control had less heparin the control in Ferguson et al. Finally, the odds ratios for McGarry et al. reflect the reduction in the risk of clinical events while the two other studies reflect a reduction in the risk of inadequate heparinization.

4. Revised Analyses by the sponsor and reviewer

In this section we examine the additional analyses provided by the applicant.

Revised definition of MI

The sponsor contends that the protocol definition of MI was specific, but insensitive. To qualify, an ischemic event needed two of the following: (1) Q-waves or left bundel branch block on EKG; (2) substantial cardiac enzyme elavations, or (3) prolonged chest pain. It has been suggested that the protocol MI definition failed to detect patients who had clinically important, though lesser degrees of ECG and enzymes. Recent publications have associated these changes with substantial morbidity and prognostic importance. As a result the sponsor re-examined the pivotal studies using a revised definition of MI. Table 4.1 summarizes the analyses of the primary endpoint with the revised MI and the protocol defined MI.

Table 4.1: bivaluridin vs. heparin: composite endpoint (procedural failure) consisting of Death. MI, Revascularization or AVC (hospitalization period)

study	Proportion of patients with procedural failure (%)				p-value (Fisher's exact)		odds ratios (95% CI)		Percent difference (bivalirudin– heparin) (95% CI)	
	MI (protocol)		revised MI							
	bivalirudin	heparin	bivalirudin	heparin	MI	revised MI	MI	revised MI	MI	revised MI
C-92-304-1	77/1071 (7.2%)	90/1060 (8.5%)	87/1071 (8.1%)	101/1060 (9.5%)	.295	.285	.835 (.61, 1.14)	.84 (.62,1.13)	-1.3% (-3.6%, 1%)	-1.4 % (-3.8%, 1%)
C-92-304-2	83/1090 (7.6%)	87/1091 (8.0%)	89/1090 (8.1%)	(100/1091) (9.1%)	.811	.447	.951 (.69, 1.30)	.89 (.66,1.20)	-.4 % (-2.7%, 1.8%)	- 1% (3.4%,1.4%)
C-92-304-1/2	160/2161 (7.4%)	177/2151 (8.2%)	176/2161 (8.1%)	20/2151 (9.3%)	.335	.178	.89 (.71, 1.11)	.86 (.70,1.06)	-.8 % (-2.4%,.8%)	-1.2% (2.9%,.5%)

Although with the new definition of MI the p-values were reduced, these p-values are still not below .05 even with the two studies combined. The confidence intervals are also very similar to those found with the protocol definition of MI.

Dropping of AVC from the primary endpoint:

The sponsor contends that the composite of death, MI and urgent revascularization reflects clinical outcomes more direct that the "procedural failure" endpoint specified in the protocol. The definition of "procedural" included abrupt vessel closure (AVC). The sponsor also contends that the determination of AVC was subjective and relied on interpretation of subtle angiographic findings by the individual treating physician. The applicant has stated that protocols for antithrombin or antiplatelet drugs no longer use AVC as an endpoint. Instead, assessments of death, MI, and urgent revascularization have become standard in cardiovascular clinical trials. Table 4.2 summarizes the analyses of the composite endpoint consisting of death, MI or revascularization with revised MI and protocol defined MI.

Table 4.2: bivaluridin vs. heparin: composite endpoint (procedural failure) consisting of Death or MI or Revascularization (hospitalization period)

Study	Proportion of patients with procedural failure (%)				p-value (Fisher's exact)		Odds ratios (95% CI)		Percent difference (bivalirudin-heparin) (95% CI)	
	MI (protocol)		revised MI							
	bivalirudin	heparin	bivalirudin	heparin	MI	revised MI	MI	revised MI	MI	revised MI
C-92-304-1	61/1071 (5.7%)	73/1060 (6.9%)	73/1071 (6.8%)	84/1060 (7.9%)	.284	.362	.817 (.57, 1.16)	.84 (.61, 1.17)	-1.2% (-3.3%, .9%)	-1.1% (-3.3%, 1.1%)
C-92-304-2	62/1090 (5.7%)	72/1091 (6.6%)	68/1090 (6.2%)	87/1091 (7.9%)	.422	.133	.854 (.60, 1.21)	.77 (.56, 1.08)	-1% (-3.1%, 1.1%)	-1.7% (-3.9%, .4%)
C-92-304-1/2	123/2161 (5.7%)	145/2151 (6.7%)	141/2161 (6.5%)	171/2151 (7.9%)	.165	.078	.835 (.65, 1.07)	.81 (.64, 1.02)	-1.4% (-2.5%, .4%)	-1.4% (-3%, .1%)

It is seen that even with the revised definition of MI and dropping AVC from the protocol defined primary endpoint, bivalirudin is not significantly superior to heparin even if we combine the two studies (p-value = .078).

APPEARS THIS WAY
ON ORIGINAL

Reducing the hospitalization period to seven days or earlier

The Cardiovascular and Renal Advisory Committee recommended that outcomes be measured at a specified time-point. The protocol originally measured outcomes during hospitalization, which increased inter-patient variability. Patients are observed for different lengths of time after PTCA, depending on the procedure results, complications. and need for additional care in the hospital. As a result, some lengths of stay exceeded 50 days in the pivotal studies. Normally, PTCA protocols define a specific period of observation, recording events under variable conditions - some in hospital and some out of hospitals. The applicant has proposed including events only while in hospital or at 7 days, whichever comes first. Table 4.3 summarizes analyses results for the protocol defined primary endpoint (with revised MI and protocol defined MI) for 7-day hospitalization period or earlier.

Table 4.3 (sponsor's): bivaluridin vs. heparin: composite endpoint (procedural failure) consisting of Death or MI or Revascularization or AVC (7-day hospitalization period or earlier)

Study	# of patients with procedural failure (%)				p-value (Fisher's exact)		Odds ratios		Percent difference: (bivalirudin-heparin) (95% CI)	
	MI (protocol)		revised MI							
	bivalirudin	heparin	bivalirudin	heparin	MI	revised MI	MI	revised MI	MI	revised MI
C-92-304-1	72/1071 (6.7%)	90/1060 (8.4%)	83/1071 (7.7%)	101/1060 (9.5%)	.141	.165	.78 (.56,1.07)	.80 (.59, 1.08)	-1.7% (-3.94%, .5%)	-1.8% (-4.2%, .6%)
C-92-304-2	81/1090 (7.4%)	85/1091 (7.7%)	87/1090 (8%)	98/1091 (9%)	.809	.442	.96 (.70, 1.32)	.89 (.65, 120)	-.3% (-2.52%, 1.92%)	-1% (-3.3%, 1.3%)
C-92-304-1/2	153/2161 (7.0%)	175/2151 (8.1%)	170/2161 (7.9%)	199/2151 (9.3%)	.206	.114	.86 (.69, 1.08)	.84 (.68, 1.04)	1.1% (-2.7%, .5%)	-1.4% (-3.0%, .3%)

It is seen that, by dropping the hospitalization period to 7-days, the rate for bivalirudin is not significantly different from heparin.

Reducing the hospitalization period to seven days (or earlier) and dropping AVC from the primary endpoint

Table 4.4 describes the analyses of the composite endpoint consisting of death, MI or revascularization when the hospitalization period is 7-days or earlier.

Table 4.4: bivaluridin vs. heparin: composite endpoint (procedural failure) consisting of Death or MI or Revascularization (seven-day period or hospitalization period, which-ever comes first)

study	Proportion of patients with procedural failure (%)				p-value (Fisher's exact)		Odds ratio (95% CI)		Percent difference (bivalirudin-heparin) (95% CI)	
	MI (protocol)		revised MI							
	bivalirudin	heparin	bivalirudin	heparin	MI	revised MI	MI	revised MI	MI	revised MI
C-92-304-1	39/1071 (3.6%)	44/1060 (4.2%)	69/1071 (6.4%)	84/1060 (7.9%)	.58	.208	.87 (.56, 1.34)	.80 (.57.1.11)	-.5% (-2.2%, 1.1%)	-1.5% (-3.7%..7%)
C-92-304-2	40/1090 (3.7%)	39/1091 (3.6%)	66/1090 (6.1%)	85/1091 (7.8%)	.909	.129	1.03 (.66. 1.61)	.77 (.55. 1.07)	.1 % (-1.5%, 1.7%)	-1.7% (-3.8%. .4%)
C-92-304-1 2	79/2161 (3.7%)	83/2151 (3.9%)	135/2161 (6.2%)	169/2151 (7.9%)	.749	.043	.95 (.69.1.29)	.78 (.62. .99)	-.2 % (-1.4%, .9%)	-1.7% (-3.1%. -.2%)

It is seen that with the revised definition of MI, revised definition of the primary endpoint (dropping AVC) and reducing the hospitalization period to 7-day, only reaches the .05 level of significance for the pooled results. It should be noted that for single studies (or pooled analyses) a p-value less than .001 is generally recommended.

5. Conclusions

1. The information provided in this resubmission has not contributed to our understanding (statistically) of the effects of heparin when used with PTCA.

2. The applicant has not established that bivalirudin is significantly better than heparin for the revised definition of the primary endpoint (dropping AVC, revised definition of MI, and reduction the hospitalization period to 7-day or earlier). Further, these modifications of the primary endpoint and combining two studies after looking at the data are not acceptable from a statistical point of view.

3. The studies submitted indicate, based on upper bounds of the confidence intervals in Table 1.3, that bivalirudin is no more than 1-2% less effective than heparin (approximately 10-25% relative). However, the two pivotal studies were not designed as non-inferiority or equivalence trials. Therefore, an equivalence/noninferiority margin was not specified in the protocol. In addition, heparin (active control in this submission) is not approved for use in PTCA. Further, the protocols allowed patients in both study arms to receive heparin after discontinuation of study treatment. For these reasons, the sponsor has been unable to establish statistically (i.e., what margin to exclude) that the confidence intervals presented support the efficacy of bivalirudin.

/S/

M. Mushfiqur Rashid. Ph.D.
Mathematical Statistician 10/13/99

Concur:

Dr. Flyer /S/ 10/13/99

CC: Archival NDA # 20873
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HFD - 180/ Mrs. DuBeau
HFD - 180/ Dr. Robie-Suh
HFD - 715/ Dr. Welch
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References

1. Narins C.R. et al. (1996). Relation between activated clotting time during angioplasty and abrupt closure circulation, vol 93, 667-671.

2. McGarry T.F. et al. (1992). The relationship of anticoagulation level and complications after successful percutaneous transluminal coronary angioplasty, American Heart Journal, vol 123, 1445.

3. Ferguson, J.J. et al. (1994). Relation between procedural activated coagulation and outcome after percutanous transluminal coronary angioplasty, Journal of American College of Cardiol., vol 23, 1061 - 1065.

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-873

Drug: Hirulog (bivalirudin) Injectio_

OCT - 2 1998

Drug Class: 1S

Indication: Anticoagulant for patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for the treatment of unstable angina.

Sponsor: The Medicines Company

Clinical Reviewer: Kathy Robie-Suh, M.D., Ph.D., HFD-180

Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Documents Reviewed: Volumes: 1.1 - 1.2, 1.50 - 1.64, 1.71 - 1.80, 1.88 - 1.149 and 1.190 - 1.193, dated December 23, 1997.

User Fee Due Date: December 22, 1998.

1. Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a potentially life-saving procedure in patients with unstable angina. The procedure cannot be performed safely in the absence of anticoagulation. According to documentation by the sponsor, published data and extensive clinical experience have established Heparin as an effective anticoagulant. Furthermore, Heparin is used to some extent in virtually all patients undergoing PTCA, and although its effectiveness for anticoagulation has long been noted (though not approved for PTCA for the treament of unstable angina), Heparin has some drawbacks. It is a heterogeneous group of mucipolysaccharides, that is not active against clot-bound thrombin. Depending on its variable binding to antithrombin III, it is antigenic and its use requires monitoring of coagulation parameters for titration dose. Hirulog is a direct thrombin inhibitor and is a homogeneous 20 - amino acid peptide which is active against-bound and circulating thrombin. With this as the scientific basis, the sponsor conducted two double blind, Heparin-controlled randomized trials of over 4,000 patients undergoing PTCA in support of Hirulog as an anticoagulant.

The objective of these studies is to demonstrate the safety and efficacy of Hirulog versus Heparin in patients undergoing PTCA for the treatment of unstable angina. The sponsor's intent was to show superiority or non-inferiority of Hirulog over Heparin

during PTCA for the treatment of unstable angina. In this study, Heparin was chosen as the comparator product for the evaluation of Hirulog. Although not specifically labeled for PTCA, the sponsor claims that heparin is indicated as an anticoagulant in a variety of interventional settings, including arterial and cardiac surgery, and has been routinely administered during PTCA since the first procedure was performed in 1970s. However, no prospective, placebo-controlled trials have been performed to determine the effectiveness of heparin as an anti-coagulant during PTCA for the treatment of unstable angina.

1.1 Studies C92-304-1 and C92-304-2:

There are two Phase III studies in this submission (C92-304-1 and C92-304-2). Both study C92-304-1 and C92-304-2 are multi-center, double blind, randomized clinical trials. The purpose of either study is to compare the safety and efficacy of Hirulog versus Heparin in patients with unstable angina for percutaneous transluminal coronary angioplasty (PTCA). Note that Heparin is not approved for this indication.

A total of 118 sites participated in the two studies, 73 in study C92-304- 1 and 45 in study C92-304-2. The disposition of sites among participating countries is given in Table 1.1 below.

Table 1.1 (Reviewer's table) : Site Decomposition in studies C92-304-1 and C92-304-2

Study #	# of Sites	# of Sites by Country								
		Engl	USA	Netherl	Belgium	Canada	France	Germany	Switzerl	Ireland
C92-304-1	73	2	64	2	1	1	2	0	1	0
C92-304-2	45	1	39	0	0	1	1	2	0	1

Note: Engl: England; Netherl: Netherland; Switzerl: Switzerlnad

Diagnosis and Main Criteria of Inclusion:

In both studies, male and female patients (at least 21 years old) who suffered from unstable angina and prequalified for PTCA were eligible for study participation. The patients were required to provide written consent. Unstable angina was defined as either:

1) a new onset of severe or accelerated angina or ischemic chest pain within the prior month, developing in the absence of an extra-cardiac condition; or

2) angina or ischemic rest pain developing between 4 hours and 2 weeks after an acute myocardial infarction (MI). To be considered eligible for the study, patients who presented following an MI must have developed ischemic pain following an

ischemic-free period at least for four hours.

Test Product, Dose and Mode of Administration:

Hirulog was administered by IV infusion, as follows:
2.5 mg/kg/h for four hours, followed by 0.2 mg/kg/hr for 14-20 hours administered immediately after starting the first infusion but just prior to PCTA. An IV bolus of 1 mg/kg was administered immediately after starting the first infusion but just prior to PTCA. To maintain the blind, patients were also given matching placebo bolus doses at 5 minutes and at 45 minutes if the measured activated clotting times (ACT) was less than 350 seconds.

The duration of treatment was 18-24 hours.

Reference Therapy, Dose and Mode of Administration:

Heparin was administered by IV infusion, as follows:
15 U/kg/h for 18-24 hours followed by an IV bolus of 175 U/kg administered immediately after starting the infusion but just prior to PTCA. The Heparin infusion was administered as 2 distinct infusions (0 to 4 hours and 4 to 18-24 hours) in order to maintain the blind. Additional IV boluses of 60 U/kg were administered at 5 minutes if the measured ACT was less than 350 seconds. Heparin was dispensed from the stock of each center's pharmacy.

Study Endpoints:

In both studies, the primary efficacy endpoint was the composite endpoint "procedural failure" defined as the occurrence of any one of the following:

1) Death, occurring during hospitalization;
2) Documented MI, not present on enrollment, occurring during hospitalization; MI was confirmed if at least 2 of the following 3 criteria were present:
   a) prolonged angina (>30 minutes)
   b) total creatine phosphokinase (CK or CPK) elevation greater or equal to 2 times the upper limit of normal and CK-MB greater than 4%
   c) new development of 2-step Minnesota q-wave codes or new left bundles branch block (not rate-related)
3) Clinical deterioration of cardiac origin in a patient's status during hospitalization requiring revascularization (angioplasty or coronary artery bypass graft (CABG)) or placement of an aortic counterpulsion balloon; and
4) Angiographic evidence of decreased coronary blood flow in the form of either established or impending abrupt vessel closure (AVC).

The occurrence of MI was confirmed by ECL. AVC during the PTCA procedure was

confirmed by the angiography core laboratory (ACL).

Secondary efficacy endpoints were:

1) the incidences of the individual components of procedural failure;
2) the incidence of procedural failure in patients who received continuous infusions of Heparin within 1 hour prior to study drug administration and
3) The occurrence of clinical events (death, MI, symptom-necessitated coronary angiography, symptom necessitated revascularization PTCA/CABG, ischemic pain requiring re-hospitalization and evidence of restenosis).

Sample Size Estimation/Randomization Schemes and Study Conduct:

In both studies, sample of sizes of 2000 evaluable patients were planned in order to detect, with at least 80% power, and a type I error rate (two-sided) of 5%, a 33% reduction in the Hirulog event rate from Heparin event rate. Note that the sample size estimation procedure (two-sample test for equality of two population proportions) did not incorporate covariates used in the primary analysis of efficacy data.

Patients with unstable angina were screened for inclusion in the study and written consent was obtained. Eligible patients were randomized in a 1:1 ratio to receive Hirulog or Heparin. Treatment assignment was double blinded. The randomization was stratified on the basis of whether the patient had experienced an acute myocardial infarction (MI) within 4 hours to 2 weeks prior to randomization, creating the Post-MI and Non-Post MI strata. All patients underwent PTCA according to the center's usual procedures. Patients randomized to the Hirulog treatment group received a two-stage, weight adjusted intravenous (IV) infusion of Hirulog and one weight adjusted bolus dose of Hirulog, beginning just prior to PTCA. Patients randomized to the Heparin treatment group received a one stage, weight adjusted IV infusion of Heparin and 1 to 3 weight adjusted bolus doses of Heparin during PTCA. The second and third bolus doses of Heparin were administered only if a patient's ACT was <350 seconds at 5 minutes (juts prior to PTCA) and /or at 45 minutes (if PTCA was still ongoing). In order to maintain the blind, ACT values were measured in all patients, regardless of treatment assignment, and patients in the Hirulog group received bolus doses of placebo for ACT values <350 seconds. For all patients, the study drug infusion was continued for a total of 18 to 24 hours, or until the patient reached an endpoint.

All patients received aspirin, 325mg daily (300mg daily in Europe) before and after the PTCA procedure. The PTCA procedure was recorded on cine film for review at an angiography core laboratory (ACL). ECGs, enzyme levels, and chest pain episodes recorded during hospitalization were reviewed by an ECG core laboratory (ECL). Arterial sheaths remained in place throughout the infusion period of the study and investigators were instructed not to remove sheaths within 2 hours after discontinuation of study drug.

Patients were monitored throughout the PTCA procedure and hospitalization for the occurrence of the composite endpoint "procedural failure." Patients also were monitored for bleeding events and other adverse events during hospitalization. Patients were contacted 3 months and 6 months after randomization to ascertain clinical status and to document the occurrence of clinical events since hospital discharge.

The following table shows patient disposition for studies C92-304-1 and C92-304-2.

Table 1.2 (Reviewer's Table): Patient Disposition

Population	# of Centers	Designs	# of Patients Randomized		Drug Group	Treated Sample Size(%)		
			Hirulog	Heparin		Post-MI	Non-Post MI	Total
C92-304-1	73	DB, Multi-Center, R	1150	1168	Heparin	203 (19)	857 (81)	1060
					Hirulog	206 (19)	865(81)	1071
C92-304-2	45	DB, Multi-Center, R	1182	1172	Heparin	169 (16)	922 (84)	1090
					Hirulog	163 (15)	927 (85)	1091

Note: DB: Double Blind; R: Randomized

It can be seen that of the 2318 patients randomized in study C92-304-1, actually 2131 (92%) received treatment drugs. These patients (who received the treatment drugs) comprise the ITT population, as defined by the protocol. Disposition information (reasons that study drug was not given) was not collected for the 187 patients (97 patients in Hirulog and 90 patients in Heparin) who were randomized but did not receive a study drug.

Demographic characteristics, for study C92-304-1, are summarized in Table A.1 in the Appendix. Study patients were predominantly male (Hirulog 68% and Heparin 66%) and white (Hirulog 90% and Heparin 91%). The treatment groups did not differ significantly with respect to gender distribution, or weight. No notable differences in these characteristics among analysis groups (All patients, Non-Post MI patients, and Post-MI patients) were evident. However, patients randomized to the Hirulog treatment group were slightly older than patients randomized to the Heparin treatment group (Hirulog mean age, 62.3 years and Heparin mean age 61.0 years, ITT population, all patients). This difference was statistically significant (p-value = .008). The age difference was also significant in the Non-MI analysis group (p-value=0.016), but not for Post-MI patients. The difference in the percentages of patients < 65 years of age and greater or equal to 65 years of age was significant only for the all patients analysis groups (p-value =. 017).

Of the 2354 patients randomized in study C92-304-2, 2181 patients(93%) actually

received treatment drug. These patients, who received the treatment drugs, comprise the ITT population, as defined by the protocol. Disposition information (reasons that the study drugs were not given) was not collected for the 173 patients (81 in Hirulog group and 92 in Heparin group) who did not receive study drug.

Study patients were predominantly male (Hirulog, 67% and Heparin, 70%) and white (Hirulog, 93% and Heparin, 91%). The treatment group did not differ significantly with respect to gender distribution, race distribution, age, or weight. No significant differences in these characterstics among analysis groups (ITT patients, Non-post-MI patients and Post-MI patients) were evident.

Safety:

In both studies, the primary safety endpoint was clinically significant bleeding. All bleeding events were classified by the investigator as major or minor. Bleeding was classified as major if it was 1) intracranial, 2) retroperitoneal, 3) clinically overt leading to transfusion of 2 or more units of blood.

Other safety measurements included monitoring of adverse events, pre- and post-treatment clinical laboratory evaluations, and monitoring of vital signs.

1.2 Sponsor's Analysis and Method

1.2.1 Data Set Analyzed by the Sponsor

All efficacy and safety data were summarized for all patients and for the two strata defined at randomization (Post-MI Patients and Non-Post-MI Patients). However, analyses of the data by strata were not mentioned in the protocol. Efficacy data were summarized and analyzed for the ITT population and the evaluable population. Safety data were evaluated for the ITT population only. The main objective of the studies is to demonstrate that Hirulog is a more effective and safer anticoagulant than Heparin for PTCA procedure for the treatment of unstable angina.

1.2.2. Reviewer's /Sponsor's Analysis and Comments

Analysis of Rates Based on the Primary Endpoint:

Efficacy:

As specified in the protocol, the sponsor assessed the treatment group differences in the incidence of procedural failure using the likelihood ratio test from logistic regression. According to the protocol, the model (main effects) was adjusted for the following covariates: site, post-MI group, age (<65, greater or equal to 65), multi-vessel disease, pre-procedural percent stenosis, and treatment. Odd ratios (Hirulog/Heparin) of procedural failure and 95% confidence intervals (CI) were obtained from the logistic regression model. The sponsor's statistical analysis of the efficacy data for evaluable patients was similar to the analyses of the ITT population. This reviewer performed both adjusted (based on logistic regression using the covariates: treatment, pooled site, age category, multivessel disease, percent stenosis) and unadjusted (without adjusting for these covariates) analyses for assessing the treatment group differences. In the following we describe the analyses results based on PROC GENMOD and PROC FREQ of SAS (version 6.12). This reviewer's adjusted analysis results are in agreement with the analysis results by the sponsor (Sponsor's p-values are given in parentheses in the table below) for both ITT and evaluable populations. However, this reviewer's unadjusted analysis produced different results from the adjusted analysis when the cell frequencies are very small (0,1 or 2). This reviewer also analyzed the data by gender, age group and race.

ITT Population:

Table 1.3 (Reviewer's): Incidence of Procedural Failure During Hospitalization - ITT Population

Study #	Sample Size (n)		# of Patients With Procedural Failure (%)		p-value	
	Hirulog	Heparin	Hirulog	Heparin	Adjusted (sponsor's)	Unadjusted (Fisher's exact)
C92-304-1	1071	1060	77 (7.2)	90 (8.5)	.253 (.253)	.295
C92-304-2	1090	1091	83 (7.6)	87 (8.0)	.7964 (.796)	.811

Note: Adj.: Adjusted for Covariates using logistic regression (likelihood ratio) Unadj: Unadjusted for Covariates.

From the above table it is seen from both adjusted and unadjusted analyses that the incidence of procedural failure during hospitalization in both studies C92-304-1 and C92-304-2 for the Hirulog treatment group was not statistically significantly different from the Heparin treatment group. Thus the superiority claim being sought by the sponsor is not supported by primary analysis results.

Post-MI Population:

The patients in studies C92-304-1 and C92-304-2 were stratified according to the presence or absence of post-infarction angina, creating the Post-MI and Non-Post MI randomization strata, respectively. This stratification was intended only to enable balanced randomization between treatment groups. As mentioned earlier, the protocols did not specify any analyses to be performed on these strata. However, the sponsor observed differential effects of study drug in the patients with and without post-infarction angina. In order to display these effects clearly, results for Post-MI ITT population are presented separately.

Table 1.4 (Reviewer's): Incidence of Procedural Failure During Hospitalization: Post-MI ITT Patients Data

Study #	Sample Size (n)		# of Patients With Procedural Failure (%)		p-value	
	Hirulog	Heparin	Hirulog	Heparin	Adjusted (sponsor's)	Unadjusted (Fisher's exact)
C92-304-1	206	203	10 (4.9)	18 (8.9)	.104(.104)	.120
C92-304-2	163	169	9 (5.5)	22 (13.0)	.017(.018)	.023

Note: Adj.: Adjusted for Covariates using logistic regression (likelihood ratio) Unadj: Unadjusted for Covariates.

It is seen from both adjusted and unadjusted analyses that, among Post-MI patients, the incidence of procedural failure during hospitalization was lower in the Hirulog treatment group compared to the Heparin treatment group in both studies. However, this difference was statistically significant (at the nominal .05 level) in study C92-304-2 only and not in study C92-304-1.

Nonpost-MI Population:

In the following we describe the analysis of incidence of procedural failure in nonpost-MI population.

Table 1.5 (Reviewer's): Incidence of Procedural Failure During Hospitalization: nonpost-MI ITT Patients Data

Study #	Sample Size (n)		# of Patients With Procedural Failure (%)		p-value	
	Hirulog	Heparin	Hirulog	Heparin	Adjusted	Unadjusted (Fisher's exact)
C92-304-1	865	857	67 (7.7)	72 (8.4)	.630	.659
C92-304-2	927	922	74(8.0)	65 (7.0)	.431	.481

Note: Adj.: Adjusted for Covariates using logistic regression (likelihood ratio) Unadj: Unadjusted for Covariates.

It is seen from the above table that there are no significant differences in incidence of procedural failures between the two treatment groups in either of the two studies.

Analysis Results by Odd Ratios with respect to ITT, Post-MI and Nonpost_MI Populations:

In the following table we present the odd ratios and the corresponding 95% confidence intervals based on procedural failures in both studies for the ITT population and Post -MI subpopulation.

Table 1.6 (Reviewer's table): Odds Ratios Based on Procedural Failures for ITT Population

Study #	Odds Ratio		95% CI for Odds Ratio All ITT Population	
	Unadj.	Adj.	Unadj.	Adj.
C92-304-1	.835	.831	(.608, 1.146)	(.604, 1.142)
C92-304-2	.951	.959	(.695, 1.301)	(.700,1.314)

Note: Unadj: Unadjusted for Covariates; Adj.: Adjusted for Covariates using logistic regression; CI: Confidence Interval

It is seen that, among all ITT patients, the risk of procedural failure was similar in the two treatment groups in both studies for the ITT population (95% CIs includes 1). Similar results were obtained for post-MI in study C92-304-1. However, for the post-MI subgroup of patients for study C92-304-2, the risk of procedural failure in was significantly lower in the Hirulog group (95% CIs exclude 1) than in the Heparin group.

In the following we present odds ratios and corresponding 95% confidence intervals for both studies for the nonpost-MI subgroup.

Table 1.7 (Reviewer's table): Odds Ratios Based on Procedural Failures for Nonpost-MI patients and Post-MI Patients

Study #	Odds Ratio				95% CI for Odds Ratio Nonpost MI Population		95% CI for Odds Ratio Post-MI Population	
	Nonpost MI		Post-MI					
	Unadj.	Adj.	Unadj.	Adj.	Unadj.	Adj.	Unadj.	Adj
C92-304-1	.922	.917	.524	.518	(.670 , 1.268)	(.647 ,1.304)	(.238, 1.154)	(.231, 1.161)
C92-304-2	1.132	1.15	.39	.387	(.822 , 1.56)	(.812 ,1.628)	(.178, .857)	(.171, .877)

Note: Unadj: Unadjusted for Covariates; Adj.: Adjusted for Covariates using logistic regression; CI: Confidence Interval

It is seen that each of the confidence intervals for the odds ratios in both studies includes unity, indicating no significant differences in the risk of procedural failures

between the two drugs in nonpost-MI population in either study. The odd ratios are in fact greater than unit in study C92-304-2 for nonpost-Mi patients, indicating numerically higher incidence rates in the Hirulog treatment group.

Analysis by Gender:

In the following table we summarize the incidence of procedural failure by gender.

Table 1.8 (Reviewer's table): Incidence of Procedural Failure by Gender for the ITT population

Study #	Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
	Male		Female		Male		Female		Male		Female	
	Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
C92-304-1	731	698	340	362	51(6.98)	58(8.31)	26(7.65)	32 (8.84)	.365	.370	.497	.586
C92-304-2	733	763	357	328	48(6.55)	58(7.60)	35(9.8)	29(8.84)	.448	.481	.684	.695

Note: Hi: Hirulog; He: Hepatin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

We observe from the above table that there are no significant differences in the incidence of procedural failure between the Hirulog treated group and the Heparin treated group among patients of either sex. A numerically higher Hirulog failure rate among females is indicated in study C92-304-2, however.

This reviewer analyzed the post-MI population of study C92-304-2 by gender. The results are summarized in the following table.

Table 1.9 (Reviewer's table): Incidence of Procedural Failure by Gender for the Post-MI ITT population by Gender in Study C92-304-2

Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
Male		Female		Male		Female		Adjusted		Unadjusted	
HI	He	Hi	He	Hi	He	Hi	He	Male	Female	Male	female
113	122	50	47	7(6.19)	13(10.66)	2(4.0)	9(19.15)	.2572	.0121	.249	.025

Note: Hi: Hirulog; He: Hepatin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

There is a significant difference between the Hirulog treated group and Heparin treated group in female popultion of the post-MI subgroup of the ITT population. Thus the

superiority of Hirulog over Heparin in post-MI subpopulation in study C92-304-2 is driven by the female population (29.21% of the post-MI population) only.

Analysis by Age Group:

In the following table we summarize the incidence of procedural failure by age group.

Table 1.10 (Reviewer's table): Incidence of Procedural Failure by Age Group

Study #	Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
	Age<65		Age >=65		Age<65		Age >=65		Age<65		Age >=65	
	Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
C92-304-1	576	624	495	436	40(6.94)	54(8.65)	37(7.47)	35 (8.26)	.284	.284	.664.	.714
C92-304-2	618	609	472	482	48(7.77)	52(8.54)	35(7.42)	35(7.26)	.688.	.677	.999	1.0

Note: Hi: Hirulog; He: Hepatin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

We observe from the above table that there are no significant differences in the incidence of procedural failure between the Hirulog treated group and the Heparin treated group among patients of either age group in any of the two studies.

Analysis by Race:

In the following table we summarize the incidence of procedural failure by race (white or nonwhite).

Table 1.11 (Reviewer's table): Incidence of Procedural Failure by Race

Study #	Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
	White		Nonwhite		White		Nonwhite		White		Nonwhite	
	Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
C92-304-1	964	964	107	96	70(7.26)	82(8.51)	7(6.54)	8(8.33)	.298	.353	.668	.789
C92-304-2	1010	992	80	99	79(7.82)	81(8.17)	4((5.0)	6(6.08)	.808	.805	.867	1.0

Note: Hi: Hirulog; He: Hepatin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

We see from the above table that there are no significant differences between the

Hirulog treated group and the Heparin treated group in either race in both studies.

Analyses Based On Secondary Endpoints:

The following table shows the incidence of individual components of procedural failure during hospitalization for the ITT population for both studies.

Table 1.12(Reviewer's table): Incidence of Individual Components of Procedural Failure During Hospitalization: ITT Population

Study #	n		Individual Component														
			Death (%)			MI (%)			Revascularisation (%)			EAVC(%)			IAVC (%)		
	Hi	He	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p
C92-304-1	1071	1060	3 (.3)	1 (.1))	.302	21 (2)	28 (2.6)	.312	49 (4.6)	65 (6.1)	.099	22 (2.1)	29 (2.7)	.325	8 (.7)	9 (.8)	.829
C92-304-2	1090	1091	6 (2.5)	5 (2.6)	.68	23 (.6)	24 (.5)	.891	47 (2.1)	57 (2.2)	.334	23 (4.3)	24 (5.2)	.935	11 (1)	2 (.2)	.008

Note: Hi: Hirulog; He: Heparin; p: p-value (adjusted for covariates using logistic regression, likelihood ratio); EAVC: Established Abrupt Vessel Closure; IAVC: Impending Abrupt Vessel Closure.

It is seen from the above table, for the ITT patient population, the incidences of death were numerically higher in the Hirulog group compared to Heparin group in both studies. Although, the incidences of other components were numerically lower in the Hirulog group than in the Heparin group in both studies, only IAVC group in study C92-304-2 was significantly different.

The following table shows the incidence of individual components of procedural failure during hospitalization for Post-MI patients in both studies. Because of very small frequencies (0, 1 or 2) in some components, the Fisher's exact test was used.

Table 1.13 (Reviewer's table) Incidence of Individual Components of Procedural Failure During Hospitalization: Post-MI Patients

Study #	n		Individual Component														
			Death (%)			MI (%)			Revascularization (%)			EAVC (%)			IAVC (%)		
	Hi	He	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p
C92-304-1	206	203	0 (0)	1 (.34)	.496	0 (0)	7 (3.4)	.0007	7 (3.4)	10 (4.9)	.469	3 (1.5)	7 (3.4)	.218	2 (1.0)	3 (1.5)	.684
C92-304-2	163	169	0 (0)	2 (1.2)	.449	2 (1.2)	7 (4.1)	.174	4 (2.5)	14 (8.3)	.027	3 (1.8)	3 (1.8)	1.0	2 (1.2)	0 90)	.240

Note: Hi: Hirulog; He: Heparin; p: p-value (Fisher's exact); EAVC: Established Abrupt Vessel Closure; IAVC: Impending Abrupt Vessel Closure.

Because of small frequencies (0,1,2) in some cells, the Fisher's exact test was used by this reviewer. For the Post-MI subgroup of patients, the incidences of each component

of procedural failure were numerically lower (except for IAVC in study C92-304-2) in the Hirulog group compared to the Heparin group in both studies. Although the difference between treatment groups in the incidence of MI was highly significant (p-value = .0007) in study C92-304-1, there was no significant difference (only numerical benefit) in study C92-304-2. There were numerical differences favoring Hirulog in incidences of death in both treatment groups in the two studies. It is worth noting that there were few deaths in both treatment groups for both studies.

In the following we describe the incidence of individual components of procedural failure in nonpost-MI ITT population.

Table 1.14 (Reviewer's table): Incidence of Individual Components of Procedural Failure During Hospitalization: nonpost-MI ITT Population

Study #	n		Individual Component												
	Hi	He	Death (%)			MI (%)			Revascularisation (%)			EAVC (%)			IAVC (%)		
			Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p
C92-304-1	865	857	3 (.35)	0 (0)	.25	21 (2.43)	21 (2.45)	1.0	6 (.69)	6 (.7)	1.0	19 (2.20)	22 (2.57)	.639	6 (.69)	6 (.7)	.1.0
C92-304-2	927	922	6 (.65)	3 (.33)	.507	21 (2.27)	17 (1.84)	. 891	47 (2.1)	57 (2.2)	.334	20 (2.16)	21 (2.28)	876	9 (.97)	2 (.22)	.065

Note: Hi: Hirulog; He: Heparin; p: p-value (Fisher's exact); EAVC: Established Abrupt Vessel Closure; IAVC: Impending Abrupt Vessel Closure.

Because of small frequencies (0, 1 or 2) in some components, the Fisher's exact test was used by this reviewer. It is seen that for nonpost-MI subgroup, there are no significant differences between the two drugs with respect to all components of the procedural failure. Except for revascularization (in C92-304-2) and EAVC, Hirulog was numerically worse than Heparin for all components in both studies.
In particular, Hirulog was numerically worse than Heparin in both studies for death and numerically worse or MI in study C92-304-2.

1.2 Reviewer's Integrated Summary of Efficacy

This reviewer conducted the Breslow-Day test for homogeneity (p-value .566) of odds ratios of two studies for the ITT population, Post-MI ITT population and Non-Post MI ITT population. The results of the tests are summarized in the following table.

Table 1.15 (Reviewer's Table) : Breslow-Day tests for homogeneity of odds ratios in study C92-304-1 and C92-304-2 for ITT, Post-MI and Nonpost-MI Populations

Population	Sample Size	Breslow-Day statistic	p-value
ITT	4312	.329	.566
Post-MI ITT	741	.259	.611
Non-Post MI ITT	3571	.794	.371

The results summarized in the table above indicated no significant difference in odds ratios between the two studies with respect to incidence of procedural failure during hospitalization. Thus the results are combinable.

In the following table we summarize the incidences of procedural failures during hospitalization for the ITT population and Post-MI population after combining the data sets from both studies.

Table 1.16 (Reviewer's table): Incidence of Procedural Failure During Hospitalization (Post-MI Patients, Nonpost MI Patients and ITT Population) - Studies C92-304-1 and C92-304-2 Combined

Population	n		# of Patients With Procedural Failure (%)		p-value	
	Hirulog	Heparin	Hirulog	Heparin	Adjusted (sponsor's)	Unadjusted (Fisher's exact)
ITT	2161	2151	160 (7.4)	177 (8.2)	.313 (.313)	.335
NonPost-MI	1792	1779	141 (7.87)	137 (7.7)	.8364	.901
Post-MI	369	372	19 (5.15)	40 (10.75)	.004 (.004)	.006

We observe that, although Hirulog is shown superior to Heparin only in the Post-MI subpopulation, a numerical benefit is indicated in the ITT population only and no Hirulog advantage is indicated in the nonpost-MI population.

Analysis by Gender:

In the following we summarize the incidence of treatment failure by gender.

Table 1.17 (Reviewer's table): Incidence of Procedural Failure by Gender

Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
Male 2925		Female 1387		Male		Female		Male		Female	
Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
1464	1461	697	690	99(6.76)	116(7.94)	61(8.75)	61(8.84)	.241	.229	.898	1.0

Note: Hi: Hirulog; He: Heparin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates

We observe from the above table that there are no significant differences in the incidence of procedural failure between the Hirulog treated group and the Heparin treated group.

In the following we summarize the incidence of treatment failure by age group.

Table 1.18 (Reviewer's table): Incidence of Procedural Failure by age group.

Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
Age <65 2427		Age>=65 1885		Age <65		Age >=65		Age <65		Age >=65	
Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
1194	1233	967	918	88(7.67)	106(8.60)	72 (7.45)	71(7.73)	.279	.295	.759	.862

Note: Hi: Hirulog; He: Heparin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates

We observe from the above table that there are no significant differences in the incidence of procedural failure between the Hirulog treated group and the Heparin treated group among patients of either age group.

Analysis by Race:

In the following we summarize the incidence of treatment failure by race.

Table 1.19 (Reviewer's table): Incidence of Procedural Failure by Race

Sample Size				# of Patients With Incidence Procedural Failure (%)				p-value			
White 3930		Nonwhite 382		White		Nonwhite		White		Nonwhite	
Hi	He	Hi	He	Hirulog	Heparin	Hirulog	Heparin	Adj	Unadj	Adj	Unadj
1974	1956	187	195	149(7.55)	163(8.33)	11(5.88)	14(7.18)	.351	.376	.577	.682

Note: Hi: Hirulog; He: Heparin; adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates

We observe from the above table that there are no significant differences in the incidence of procedural failure between the Hirulog treated group and the Heparin treated group in either race.

In the following table we summarize incidence of individual components of procedural failure.

Table 1.20 (Reviewer's table): Incidence of Individual Components of Procedural Failure During Hospitalization: ITT Population, Post-MI Patients and Nonpost-MI Patients - Studies C92-304-1 and C92-304-2 Combined

Popl	n		Individual Component													
	Hi	He	Death (%)			MI (%)			Revascularization (%)			EAVC (%)			IAVC (%)	
			Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p	Hi	He	p
ITT	2161	2151	9 (.4)	6 (.3)	.415	44 (2)	52 (2.4)	.41	96 (4.4)	122 (5.7)	.071	45 (2.1)	53 (2.5)	.418	19 (.9)	11 (.5)	.199
Post-MI	369	372	0 (0)	3 (.8)	.249	2 (.5)	14 (3.8)	.0038	11 (3)	24 (6.5)	.036	6 (1.6)	10 (2.7)	.45	4 (1.1)	3 (.8)	.724
Nonpost MI	1792	1779	9 (.5)	3 (.17)	.145	42 (2.34)	38 (2.14)	.735	85 (4.74)	98 (5.51)	.324	39 (2.18)	43 (2.42)	.656	15 (.84)	8 (.45)	.209

Note: Popl: Population; Hi: Hirulog; He: Heparin; p: p-value unadjusted (Fisher's exact); EAVC: Established Abrupt Vessel Closure; IAVC: Impending Abrupt Vessel Closure.

The above table shows that there are significant differences between the two treatment groups for MI and revascularization in Post-MI subgroup of patients in favor of Hirulog. It should be noted here that there were numerically more deaths in the Hirulog treated group than in the Heparin treated group for both the ITT and nonpost MI populations. Because of very small frequencies (0, 1 or 2) in some components, the Fisher's exact test was used.

1.3 Sponsor's Safety Event Summary Results and Reviewer's Comments:

This reviewer compared the occurrence of bleeding events by the likelihood ratio test (based on a logistic regression model (main effects) with covariates for treatment, site; Post-MI group, age (<65, greater or equal to 65), multi-vessel disease, and pre-procedural percent stenosis) and Fisher's exact test (not adjusted for covariates). This reviewer's analysis results are consistent with the analysis results by the sponsor.

Both the incidence of major bleeding and the time to first occurrence of major bleeding significantly favored Hirulog over Heparin in all analysis groups in both studies. In both studies, significant differences in favor of Hirulog were also seen for any bleeding.

In the following table we summarize bleeding events according to major bleeding (treatment emergent) and any bleeding (treatment emergent).

Table 1.21 (Reviewer's table): Incidence of Treatment-Emergent Bleeding (ITT Population)

Study #	Sample Size		# of Patients With Treatment-Emergent Bleeding (%)				p-value			
	Hirulog	Heparin	Major		Any		Major Bleeding		Any Bleeding	
			Hirulog	Heparin	Hirulog	Heparin	Adj.	Unadj	Adj	Unadj
C92-304-1	1071	1060	47 (4)	113 (11)	593 (55)	864 (82)	.0001	<.0001	0001	<.0001
C92-304-2	1090	1091	32 (3)	86 (8)	561 (51)	835 (77)	.0001	<.0001	0001	<.0001

Note: adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

Premature discontinuations and temporary discontinuations of study drug, as well as study drug dose reductions due to bleeding events, were less common in the Hirulog group than in the Heparin group in both studies. Hirulog and Heparin treatment groups were similar with respect to the overall incidence of treatment emergent non-bleeding adverse events and with respect to the severity of these events.

Serious adverse events were uncommon (2%) in both the Hirulog and Heparin treatment groups. The incidence of in-hospital death was low (<1%) in both the Hirulog and Heparin treatment groups.

Post-MI and Nonpost-MI ITT Population

Post-MI ITT Population:

In the following table we summarize the treatment emergent bleeding events (major and any) for post-MI population.

Table 1.22 (Reviewer's table): Incidence of Treatment-Emergent Bleeding for post-MI (ITT Population)

Study #	Sample Size		Treatment-Emergent Bleed(%)				p-value			
	Hirulog	Heparin	Major		Any		Major Bleed		Any Bleed	
			Hirulog	Heparin	Hirulog	Heparin	adj	unadj	adj	unadj
C92-304-1	206	203	8(3.88)	25(12.32)	118 (57)	151(74)	.0005	.0018	0001	.0003
C92-304-2	163	169	1(.61)	19(11.24)	78(48)	115(68)	.0001	<.0001	.0002	.0002

Note: adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

It is seen from the above table that there were significant differences in favor of Hirulog in major bleeding (treatment emergent) and any bleeding (treatment emergent) events between Hirulog treated group and Heparin treated group for the post-MI ITT population.

Nonpost-MI Population:

In the following table we summarize the treatment emergent bleeding events (major and any) for nonpost-MI population.

Table 1.23 (Reviewer's table): Incidence of Treatment-Emergent Bleeding for nonpost-MI ITT Population

Study #	Sample Size		# of Patients With Treatment-Emergent Bleeding (%)				p-value			
	Hirulog	Heparin	Hirulog		Heparin		Major Bleed		Any Bleed	
			Major	Any	Major	Any	Adj	Unadj	Adj	Unadj
C92-304-1	865	857	39(4.51)	475(56)	88(10.27)	713(83)	.0001	<.0001	.0001	<.0001
C92-304-2	927	922	31(3.34)	483(52)	67(7.27)	720(78)	.0001	<.0001	G001	<.0001

Note: adj: adjusted for covariates using logistic regression; unadj: not adjusted for covariates.

It is seen from the above table that there were significant differences in favor of Hirulog in major bleeding (treatment emergent) and any bleeding (treatment emergent) events between Hirulog treated group and Heparin treated group for the nonpost-MI ITT population.

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1.4 Conclusions

1. For the ITT patient population, this reviewer's assessment indicates no significant difference between Hirulog and Heparin regarding the primary endpoint (procedural failure) in both study C92-304-1 and C92-304-2.

2. For the post-MI patient sub-population, the incident of procedural failure was significantly lower in the Hirulog group than in the Heparin group in study C92-304-2. A numerical trend for Hirulog over Heparin was indicated in study C92-304-1. However, it should be noted that the analysis of Post-MI subgroup (which constitutes less than 20% of the ITT population) of patients was not prospectively specified in the protocol.

3. For the nonpost-MI ITT population (almost 80% of the ITT population), there is no significant difference between Hirulog and Heparin. There is a slight numerical Hirulog advantage over Heparin in study C92-304-1, but no numerical trend of Hirulog over Heparin in study C92-304-2.

4. It should be noted that for the individual components of the composite endpoints, heparin held a numerical edge over Hirulog in the nonpost MI subgroup of patients for almost all components, especially death and MI.

5. The two studies were not designed to show non-inferiority of Hirulog to Heparin.

6. Hirulog was a significantly safer anticoagulant with respect to major bleeding (treatment emergent) than Heparin in patients with unstable angina undergoing PTCA in both study C92-304-1 and C92-304-2.

7. Because the minimum age requirement for both studies is twenty one years, the implications of these findings on patients who are less than twenty one years are unclear.

1.5 Recommendations

The protocol stated objective for this study (superiority of Hirulog over Heparin) was not achieved. Efficacy is suggested for the post-MI subgroup of patients (19% of the enrolled patient population). But this would need to be confirmed in another Phase III study. Therefore, this reviewer's recommendation is for another study to support the superiority in post-MI patients.

/S/

M. Mushfiqur Rashid 10/2/98
Mathematical Statistician

Concur:

Dr. Sankoh /S/

Dr. Welch /S/

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Table A.1 (Reviewer's): Patient's Demographic Data in Study C92-304-1

Characteristics	All Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin
Age (years):				
<65	576 (54)	624 (59)	116 (56)	132 (65)
>= 65	495 (5)	436 (41)	90 (44)	71 (35)
Gender:				
Male	731(68)	698 (66)	149(72)	132 (65)
Female	340(32)	362 (34)	57 (28)	71 (35)
Race:				
White	964 (91)	964 (91)	181 (88)	175 (86)
Non-White	107 (9)	96 (10)	25 (12)	28 (14)

Table A.2 (Reviewer's) : Patient's Demogrphic Data in Study C92-304-2

Characteristics	All Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin
Age (years):				
<65	618(57)	609(56)	97(60)	101 (60)
>= 65	472(43)	482(44)	66(40)	68 (40)
Gender:				
Male	733(67)	763(70)	113(69)	122 (72)
Female	357(33)	328(30)	50 (31)	47 (28)
Race:				
White	1010(93)	992 (91)	151 (93)	155 (92)
Non-White	80 (7)	99(9)	12 (7)	14(8)