Differences between treatment groups were even less apparent at 6-month follow-up than immediately following PTCA. Among all patients the incidence of any event was essentially the same in both treatment groups. Among post-MI patients there was a trend toward fewer events in the Hirulog as compared to the heparin patients at 6 months. For the total population numbers of deaths continued to be greater in the Hirulog patients. No formal statistical comparisons were made of this data.

G. **Safety Analysis:** For the safety analysis the sponsor has summarized and analyzed the incidence of "treatment-emergent" events, which were those events that occurred or worsened following the start of administration of study drug. Events were separated into bleeding adverse events and non-bleeding adverse events. Analyses were done only of serious adverse events, all bleeding events and major and minor bleeding events. The incidences of these events are summarized in the following table:

Study C92-304-1: Summary of Bleeding Events[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N = 1071	N = 1060	N = 865	N = 857	N = 206	N = 203
Any Bleeding Event	593 (55)	864 (82)	475 (55)	713 (83)	118 (57)	151 (74)
Any Bleeding Events Seen in ≥1% of Patients in Any Group:						
Puncture site hemorrhage	232 (22)	549 (52)	194 (22)	453 (53)	38 (18)	96 (47)
Hematuria	224 (21)	252 (24)	183 (21)	209 (24)	41 (20)	43 (21)
Cath. site ecchymosis without hematoma	152 (14)	206 (19)	118 (14)	165 (19)	34 (17)	41 (20)
Cath. site ecchymosis with hematoma	152 (14)	364 (34)	125 (14)	302 (35)	27 (13)	62 (31)
Ecchymosis	93 (9)	177 (17)	77 (9)	149 (17)	16 (8)	28 (14)
Anemia	26 (2)	35 (3)	22 (3)	27 (3)	4 (2)	8 (4)
Groin hematoma	23 (2)	36 (3)	18 (2)	31 (4)	5 (2)	5 (2)
Venipuncture site prolonged bleeding	18 (2)	48 (5)	15 (2)	37 (4)	3 (1)	11 (5)
Hematemesis	13 (1)	15 (1)	13 (2)	13 (2)	0	2 (<1)
Hemoptysis	12 (1)	16 (2)	10 (1)	9 (1)	2 (<1)	7 (3)
Other	12 (1)	33 (3)	9 (1)	28 (3)	3 (1)	5 (2)
Bleeding gums	10 (<1)	3 (<1)	10 (1)	2 (<1)	0	1 (<1)
Melena	9 (<1)	4 (<1)	6 (<1)	3 (<1)	3 (1)	1 (<1)
Epistaxsis	7 (<1)	15 (1)	6 (<1)	12 (1)	1 (<1)	3 (1)
CABG/op	6 (<1)	17 (2)	5 (<1)	16 (2)	1 (<1)	1 (<1)
Other hematoma	6 (<1)	16 (2)	6 (<1)	12 (1)	0	4 (2)
Mouth bleeding	4 (<1)	9 (<1)	4 (<1)	6 (<1)	0	3 (1)
Blood in stool	3 (<1)	8 (<1)	2 (<1)	5 (<1)	1 (<1)	3 (1)
Any Major Bleeding Event	47 (4)	113 (11)	39 (5)	88 (10)	8 (4)	25 (12)
Major Bleeding Events:						
Anemia	14 (1)	22 (2)	12 (1)	15 (2)	2 (<1)	7 (3)
Puncture site hemorrhage	14 (1)	41 (4)	13 (2)	34 (4)	1 (<1)	7 (3)
Catheterization site hematoma	6 (<1)	32 (3)	6 (<1)	25 (3)	0	7 (3)
CABG/Op	5 (<1)	14 (1)	4 (<1)	13 (2)	1 (<1)	1 (<1)
Catheterization site ecchymosis without hematoma	5 (<1)	2 (<1)	4 (<1)	2 (<1)	1 (<1)	0
Ecchymosis	4 (<1)	10 (<1)	3 (<1)	8 (<1)	1 (<1)	2 (<1)
Melena	4 (<1)	1 (<1)	3 (<1)	1 (<1)	1 (<1)	0
Gastrointestinal hemorrhage	3 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0
Groin hematoma	3 (<1)	8 (<1)	2 (<1)	8 (<1)	1 (<1)	0
Bloody chest tube drainage	2 (<1)	2 (<1)	2 (<1)	1 (<1)	0	1 (<1)
Hematuria	2 (<1)	5 (<1)	2 (<1)	4 (<1)	0	1 (<1)
Retroperitoneal bleeding	2 (<1)	7 (<1)	1 (<1)	6 (<1)	1 (<1)	1 (<1)
Hematemesis	1 (<1)	6 (<1)	1 (<1)	6 (<1)	0	0
Intracranial bleeding	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Venipuncture site prolonged bleeding	1 (<1)	5 (<1)	1 (<1)	2 (<1)	0	3 (1)
Other hematoma	0	2 (<1)	0	2 (<1)	0	0
Other major bleb	10 (<1)	7 (<1)	7 (<1)	6 (<1)	3 (<1)	1 (<1)
Any Major Bleeding Event Associated with Hemoglobin Decrease of ≥3g/dL	25 (2)	66 (6)	21 (2)	53 (6)	4 (2)	13 (6)
Any Major Bleeding Event Associated with Transfusion	24 (2)	75 (7)	18 (2)	61 (7)	6 (3)	14 (7)
Premature Discontinuations Due to Bleeding Events	18 (2)	67 (6)	6 (<1)	62 (7)	2 (1)	5 (2)
Dose Reduction Due to Bleeding Events	16 (1)	86 (8)	13 (2)	73 (9)	3 (1)	13 (6)

[a] Numbers are numbers of patients with percent of patients in parentheses

[b] Other major bleeds included in the Hirulog group, one case each of bleeding gums, coagulation disorder, eye hemorrhage, hemoptysis, hemothorax, injection site hematoma, lung hemorrhage, subarachnoid hemorrhage and ventricular rupture; in each (Hirulog and heparin) treatment group, one case of pseudo aneurysm; in the heparin group, one case each of edema and blood in stool and 4 unspecified cases of other serious bleeding.

reviewer's original table, based on sponsor's tables, NDA Vol. 1.71, pp. 311 through 339 and 369 through 378 and 392

Fifty-five percent of Hirulog patients and 82% of heparin patients experienced some bleeding after the start of study drug administration. Treatment-emergent major bleeding events occurred in 47 Hirulog patients (4%) and 113 heparin patients (11%). The percentages of post-MI patients experiencing these events were similar to those in the overall population (4% of Hirulog patients and 12% of heparin patients). The most frequent events in all treatment groups were anemia, puncture site hemorrhage, catheterization site hematoma, CABG/Op, and eccymosis. About 53% of patients in the Hirulog group and 58-66%% of patients in the heparin group having major bleeding had a hemoglobin decrease of $\geq$3g/dL and/or required transfusion. Among patients with bleeding events, the median time to first occurrence of any bleeding event was significantly longer ($p=0.001$) in the Hirulog group as compared to the heparin group (18.5 hrs vs. 7.6 hrs). Time to event (life table analysis) results were similar for major bleeding and minor bleeding and for non-post MI patients and post-MI patients except that for post-MI patients having major bleeding events, the median time to event was similar for both treatments (14.5 hrs for Hirulog and 15.5 hrs for heparin). Most of the bleeding events in both treatment groups and for non-post-MI and post-MI patients were felt by the investigator to be possibly, probably or definitely study drug related.

Nineteen Hirulog patients and 48 heparin patients had bleeding events that were classified as serious (death, life-threatening, caused or prolonged hospitalization, or caused a permanent disability). Eighteen Hirulog patients and 67 heparin patients were discontinued from the study prematurely due to bleeding events and 16 Hirulog patients and 86 heparin patients had study drug dose reduced due to bleeding events. One Hirulog patient and 4 heparin patients had study drug temporarily discontinued due to bleeding events.

Higher ACT values were associated with a greater incidence of bleeding events in both treatment groups in both non-post-MI and post-MI patients. For patients with ACT values >300, the incidence of all bleeds and major bleeds consistently tended to be greater in the heparin group than in the Hirulog group for non-post-MI and post-MI patients. Incidence of bleeding adverse events as related to ACT values is summarized in the following table:

Study C92-304-1: Numbers of Patients with Bleeding Events in Relation to ACT Values (Intent-to-Treat Population)[A]

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog N=1071	Heparin N=1060	Hirulog N=865	Heparin N=857	Hirulog N=206	Heparin N=203
Any Bleeding Event	593/1071 (55)	864/1060 (82)	475/865 (55)	713/857 (83)	118/206 (57)	151/203 (74)
Any Bleeding Event within 24 hrs	483/1071 (45)	795/1060 (75)	397/865 (46)	660/857 (77)	86/206 (42)	135/203 (67)
For All Patients with Bleeding Events within 24Hrs: Bleeding with ACT Values:						
<200	3/14 (21)	16/18 (89)	2/11 (18)	11/13 (85)	1/3 (33)	5/5 (100)
200 - 300	84/185 (45)	50/70 (71)	62/144 (43)	40/51 (78)	22/41 (54)	10/19 (53)
>300 - 350	141/329 (43)	136/179 (76)	123/273 (45)	111/142 (78)	18/56 (32)	25/37 (68)
>350	248/526 (47)	584/774 (75)	204/422 (48)	493/638 (77)	44/104 (42)	91/136 (67)
Bleeding Events without ACT Values	7/17 (41)	9/19 (47)	6/15 (40)	5/13 (38)	1/2 (50)	4/6 (67)
Any Major Bleeding Event	47/1071 (4)	113/1060 (11)	39/865 (5)	88/857 (10)	8/206 (4)	25/203 (12)
Any Major Bleeding Event within 24 hrs	29/1071 (3)	90/1060 (8)	23/865 (3)	73/857 (9)	6/206 (3)	17/203 (8)
For All Patients with Major Bleeding Events within 24Hrs: Major Bleeding with ACT Values:						
<200	0/14 (0)	1/18 (6)	0/11 (0)	1/13 (8)	0/3 (0)	0/5 (0)
200 - 300	3/185 (2)	4/70 (6)	2/144 (1)	4/51 (8)	1/41 (2)	0/19 (0)
>300 - 350	9/329 (3)	20/179 (11)	7/273 (3)	15/142 (11)	2/56 (4)	5/37 (14)
>350	16/526 (3)	63/774 (8)	13/422 (3)	52/638 (8)	3/104 (3)	11/136 (8)
Major Bleeding Events without ACT Values	1/17 (6)	2/19 (11)	1/15 (7)	1/13 (8)	0/2 (0)	1/6 (17)

[A] numbers given are number of patients and (in parentheses) percent of patients evaluated

reviewer's original table, based on sponsor's tables, NDA Vol. 1.71, pp. 349 through 354

Kaplan-Meyer survival curves of bleeding as a function of time showed a statistically significantly lower event rate for Hirulog as compared to heparin (p-value 0.001). over the 48 hours after start of study drug. Median time to occurrence of any event was 18.5 hrs for Hirulog and 7.6 hrs for heparin. Results were similar for post-MI and non-post-MI patients.

In this study 884/1071 (83%) of patients treated with Hirulog and 881/1060 (83%) of patients treated with heparin reported one or more adverse events. The most frequent adverse events were back pain, pain, headache, injection site pain, hypotension, and nausea. Thrombocytopenia was listed as an adverse event for 2 Hirulog patients and 1 heparin patient. Adverse events occurring in 5% or more of the patients in any treatment group are summarized by body system in the table below:

Study C92-304-1: Summary by Body System of Adverse Events Occurring in ≥5% of Patients in Any Group[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirul	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1071	N=1060	N=865	N=857	N=206	N=203
Any Adverse Event	884 (83)	881 (83)	707 (82)	703 (82)	177 (86)	178 (88)
Body As A Whole	688 (64)	732 (69)	547 (63)	587 (68)	141 (68)	145 (71)
Pain back	446 (42)	470 (44)	358 (41)	386 (45)	88 (43)	84 (41)
Pain	161 (15)	182 (17)	133 (15)	150 (18)	28 (14)	32 (16)
Headache	132 (12)	123 (12)	111 (13)	101 (12)	21 (10)	22 (11)
Injection site pain	86 (8)	147 (14)	71 (8)	122 (14)	15 (7)	25 (12)
Pain pelvic	56 (5)	74 (7)	46 (5)	55 (6)	10 (5)	19 (9)
Fever	55 (5)	59 (6)	39 (5)	48 (6)	16 (8)	11 (5)
Pain abdominal	50 (5)	54 (5)	45 (5)	43 (5)	5 (2)	11 (5)
Cardiovascular System	333 (31)	347 (33)	268 (31)	286 (33)	65 (32)	61 (30)
Hypotension	137 (13)	177 (17)	110 (13)	148 (17)	27 (13)	29 (14)
Hypertension	73 (7)	56 (5)	62 (7)	49 (6)	11 (5)	7 (3)
Bradycardia	62 (6)	83 (8)	54 (6)	68 (8)	8 (4)	15 (7)
Digestive System	265 (25)	288 (27)	218 (25)	235 (27)	47 (23)	53 (26)
Nausea	167 (16)	170 (16)	141 (16)	138 (16)	26 (13)	32 (16)
Vomiting	72 (7)	87 (8)	64 (7)	70 (8)	8 (4)	17 (8)
Dyspepsia	55 (5)	60 (6)	42 (5)	51 (6)	13 (6)	9 (4)
Metabolic and Nutritional Disorders	75 (7)	95 (9)	60 (7)	84 (10)	15 (7)	11 (5)
Hypokalemia	36 (3)	49 (5)	27 (3)	43 (5)	9 (4)	6 (3)
Nervous System	222 (21)	255 (24)	175 (20)	207 (24)	47 (23)	48 (24)
Insomnia	59 (6)	71 (7)	52 (6)	61 (7)	17 (8)	10 (5)
Anxiety	50 (5)	73 (7)	41 (5)	58 (7)	9 (4)	15 (7)
Dizziness	43 (4)	50 (5)	36 (4)	41 (5)	7 (3)	9 (4)
Nervousness	40 (4)	40 (4)	26 (3)	33 (4)	14 (7)	7 (3)
Respiratory System	108 (10)	105 (10)	86 (10)	79 (9)	22 (11)	26 (13)
Skin	50 (5)	62 (6)	39 (5)	47 (5)	11 (5)	15 (7)
Urogenital System	83 (8)	106 (10)	70 (8)	91 (11)	13 (6)	15 (7)
Urinary retention	39 (4)	54 (5)	32 (4)	50 (6)	7 (3)	4 (2)

[a] Numbers are numbers of patients with percent of patients in parentheses

reviewer's original table, based on sponsor's table, NDA Vol. 1.71, pp. 393 through 401

Most of the reported adverse events were not serious and most of the serious adverse events involved bleeding. Bleeding events are discussed above. Twenty patients in the Hirulog group and 21 patients in the heparin group experienced other (non-bleeding) serious adverse events. These serious events are summarized in the following table:

Study C92-304-1: Summary of Serious Non-Bleeding Adverse Events[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1071	N=1060	N=865	N=857	N=206	N=203
Any Serious Non-Bleeding Adverse Event	20 (2)	21 (2)	19 (2)	12 (1)	1 (<1)	9 (4)
Serious Non-Bleeding Events Reported in ≥2 Patients in Any Treatment Group:						
Fever	2 (<1)	1 (<1)	2 (<1)	1 (<1)	0	0
Syncope	2 (<1)	1 (<1)	2 (<1)	1 (<1)	0	0
Ventricular fibrillation	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Heart failure	1 (<1)	2 (<1)	1 (<1)	0	0	2 (<1)
Embolus	0	2 (<1)	0	1 (<1)	0	1 (<1)
Hypotension	0	2 (<1)	0	2 (<1)	0	0
Cardiogenic shock	0	2 (<1)	0	2 (<1)	0	0
Vascular anomaly	0	3 (<1)	0	3 (<1)	0	0
Cerebral ischemia	2 (<1)	1 (<1)	2 (<1)	0	0	1 (<1)
Lung edema	2 (<1)	1 (<1)	2 (<1)	0	0	1 (<1)
Kidney failure	3 (<1)	0	3 (<1)	0	0	0

[a] Numbers are numbers of patients with percent of patients in parentheses

reviewer's original table, based on sponsor's table, NDA Vol. 1.71, pp. 454 through 455

Non-bleeding serious adverse events were infrequent and no clear trends for these events for Hirulog vs. heparin were apparent.

Three patients randomized to Hirulog and 1 patient randomized to heparin died during hospitalization. The three Hirulog deaths were as follows:

- Patient #037/0570 was a 73 year old white man with history of arrhythmia and myocardial infarction about 5 weeks prior to study entry. He received one bolus of Hirulog and was started on the 4-hour infusion. He suffered abrupt vessel closure during the 4-hour infusion period, study drug was stopped and he was withdrawn from the study and coronary stents placed. The patient suffered episodes of hematuria (gross or microscopic not specified) about 1 day after discontinuation of study drug. A few days later he experienced chest pain with ECG changes and subsequently underwent PTCA to relieve a coronary artery blockage. However, he continued to deteriorate and died of cardiac arrest 4 days after study drug discontinuation. Death was judged unrelated to study drug.

- Patient #047/0507 was a 77 year old white woman with history of valvular heart disease, serum creatinine 1.3mg/dL and BUN of 20mg/dL, and elevated cholesterol without MI. On study entry she had hypertension and unstable angina. She received one bolus of Hirulog and one of placebo and the Hirulog infusion was started. During PTCA she suffered abrupt vessel closure and study drug was stopped. She underwent coronary stent placement. She experienced hematuria 16 hrs after discontinuation of study drug which resolved over an unstated period. She remained hospitalized and suffered additional adverse events including GI bleeding, congestive heart failure, coagulopathy, and ventricular fibrillation. She died of respiratory and renal failure about 3 weeks after study drug administration. Investigator judged hematuria "possibly related" to study drug; death was judged unrelated to study drug.

- Patient #111/0504 was a 69 year old white woman with history of hypertension who received a bolus of Hirulog and a bolus of placebo and had Hirulog infusion started. During PTCA she developed impending abrupt vessel closure and study drug was stopped and she was discontinued from the study. She underwent coronary artery bypass graft surgery but died of cardiogenic shock 6 days after study drug administration. Death was judged unrelated to study drug.

The one heparin patient who died in hospital was as follows:

- The heparin patient who died during hospitalization was #039/0001, a 62 year old white woman with unstable angina following an acute Q-wave MI 4 days prior to study entry. She received one bolus of heparin and heparin infusion and underwent PTCA. About 3 hours after discontinuation of study drug patient suffered chest pain and ECG changes and was found to have abrupt vessel closure and a new acute MI. About 14 hours later the patient suffered a massive intracranial hemorrhage and died. Death was judged unrelated to study drug.

An additional 14 Hirulog patients and 10 heparin patients died after hospital discharge during the 6 months follow-up period. Causes of death for the Hirulog patients were: myocardial infarction, 3; post-CABG surgery arrest or complications, 3; sudden cardiac death (heart attack), 2; respiratory failure due to adult respiratory distress syndrome, 1; pancreatic cancer, 1; stomach cancer, 1; pneumonia, 1; suicide, 1; and multiple causes, 1. Causes of death for the heparin patients were: cardiac arrest (heart attack), 3; congestive heart failure or heart failure, 2; myocardial infarction, 1; brain hemorrhage, 1; cancer, 1; post-surgical sepsis, 1; and unknown, 1.

Other than decreases in hemoglobin, hematocrit, and RBC counts (which were less in the Hirulog group as compared to the heparin group) consistent with bleeding, there were no clinically significant effects of Hirulog on measured clinical laboratory parameters.

Incidence of clinically significant low platelet counts ($<120x10_3$/uL) was the same in Hirulog patients (1.1%) and heparin patients (1.1%). In the Hirulog group 0.7% (6 patients) of patients with normal platelet counts at study entry had low counts at study completion; in the heparin group 1.0% (9 patients) of patients had a shift from normal to low platelet counts.

Though the protocol indicated that patients who had had prior exposure to Hirulog or who had participated in other blinded Hirulog studies would have plasma collected for determination of antibodies to Hirulog, no results for any determinations are given in the study report.

Reviewer's comments:
This study does not provide support for superiority of Hirulog over heparin with regard to either the primary efficacy endpoint (procedural failure) of any of the secondary endpoints in the overall population studied. Though there are suggestions of superior efficacy of Hirulog in the post-MI population (patients having postinfarction angina, angina between 4hrs and 2 weeks after suffering an acute myocardial infarction) for the secondary endpoint of myocardial infarction during hospitalization, this population is relatively small accounting for less than 20% of the patients enrolled in the study.

The disposition of patients in this study is incompletely documented. More screening numbers appear to have been used than reported patients screened. Also, about 8% of patients randomized did not receive study medication. Though the protocol explicitly stipulated that information should be collected regarding these patients, none was.

Bleeding events including major, minor and all events did appear to be less frequent in the patients who received Hirulog than in the patients who received heparin and this generally appeared to be the case even when ACT values during PTCA were taken into account.

Study C92-304-2:
The Study Report for this trial is contained in NDA Vols. 1.112 through 1.148. The study protocol is included in NDA Vol. 1.113, pp. 45 through 198.

A. **Investigators:** This study was carried out from March 24, 1993 through March 13, 1995 by Biogen at 45 sites in 6 countries (39 U.S., 2 Germany, 1 England, 1 France, 1 Canada, 1 Ireland). Investigators and study site numbers are listed below:

Study C92-304-2: Investigators

Asam Anwar, M.D. Baylor University Medical Center Dallas, TX	52	Thomas Kelly, M.D. The Moses H. Cone Memorial Hospital Greensboro, NC	60
Raoul Bonan, M.D. Institut de Cardiologie de Montreal Montreal, Quebec, Canada	01	Daniel Kolansky, M.D. Hosp. of the Univ. of Pennsylvania Philadelphia, PA	38
Warren Breisblatt, M.D. Albany Medical College Albany, NY	114	Phillip Kraft, M.D. Henry Ford Hospital Detroit, MI	62
Michael Cleman, M.D. Yale University School of Medicine/Yale-New Haven Hospital New Haven, CT	56	David Laxson, M.D. Univ. of Minnesota Medical Center Minneapolis, MN	12
Marc Cohen, M.D. Hahnemann University Philadelphia, PA	31	Conor Lundergan, M.D. George Washington University Washington, DC	40
Mark Cohen, M.D. Indiana Heart Physicians, Inc. Beech Grove, IN	02	Roger Lyons, M.D. Southwest Texas Methodist Hospital San Antonio, TX	41
Robert Feldman, M.D. Munroe Regional Medical Center Ocala, FL	34	Raymond Magorien, M.D. Ohio State University Columbus, OH	72
James Ferguson, M.D. Texas Heart Institute Houston, TX	05	Serge Makowski, M.D. Hospital Broussais Paris, France	27
Desmond Fitzgerald, M.D. Mater Misericardia Hospital Dublin, Ireland	51	David Muller, M.D. University Hospital Ann Arbor, MI	54
Martin Frey, M.D. Sarasota Memorial Hospital Sarasota, FL	71	Bruce Murphy, M.D. St. Vincent Infirmary Little Rock, AR	128
Nieca Goldberg, M.D. State University Hospital of Brooklyn Brooklyn, NY	115	Charles Orr, M.D. St. Vincent Professional Bldg. Indianapolis, IN	65
Aian Guerci, M.D. St. Francis Hospital Roslyn, NY	07	John Robb, M.D. Dartmouth-Hitchcock Medical Center Lebanon, NH	19
John Gurley, M.D. University of Kentucky Medical Center Lexington, KY	118	Mark Schweiger, M.D. Baystate Medical Center Springfield, MA	21
Larry Hattel, M.D. United Medical Center (2 locations) Cheyenne, WY	109	Neal Shadoff, M.D. New Mexico Heart Clinic Albuquerque, NM	44
Stevan Himmelstein, M.D. Cardiology Group of Memphis Memphis, TN	15	Fayaz Shawl, M.D. Washington Adventist Hospital Takoma Park, MD	123
Professor Hofling Universitat Munchen Munchen, Germany	50	David Swan, M.D. Huntington Memorial Hospital Pasadena, CA	116
Matthew Holland, M.D. V. A. Medical Center Albuquerque, NM	134	George Taylor, M.D. St. John's Hospital Springfield, IL	67

L. A. Iannone, M.D. Iowa Heart Center Des Moines, IA	36	Gerald Timmis, M.D. William Beaumont Hospital Royal Oak, MI	46
J. Dan Jackman, M.D. Mother Frances Hospital Tyler, TX	09	George Vetrovec, M.D./ Naqui Sabri, M.D. Medical Colleg of Virginia Richmond, VA	25
David Jewitt, M.D. Kings Colloge Hospital London, England	28	Linley Watson, M.D. Scott and White Hospital Temple, TX	69
Allen Johnson, M.D., F.A.C.P., F.A.C.C. Green Hospital of Scripps Clinic La Jolla, CA	59	Michael Winniford, M.D. Univ. of Iowa Hospitals and Clinics/ Iowa V. A. Medical Center Iowa City, IA	110
Professor W. Kasper St. Josefs Hospital Wiesbaden, Germany	77	Seth Worley, M.D. Lancaster General Hospital Lancaster, PA	24
Mirle Kellet, M.D. Maine Medical Center Portland, ME	10		

from sponsor's table, NDA Vol. 1.113, pp. 245 through 247

B. **Enrollment and Disposition of Patients:** A total of 8431 patients were screened. Of these, 2354 patients were randomized. Post-myocardial infarction (post-MI) patients constituted about 13% of patients screened and about 15% of patients randomized.

By my counts (based on sponsor's tables in NDA Vols. 1.123 p. 4 through 1.124, p. 319) thirteen sites enrolled more than 56 patients. These 13 sites enrolled a total of 1445 patients (about 59% of total randomized). All except one of these largest sites were located in the U.S. Six sites enrolled more than 100 patients (about 35% of total randomized). There were 362 post-MI patients enrolled. These represented about 15% of total patients enrolled. Four sites enrolled 112 post-MI patients (about 31% of post-MI patients enrolled).

At most sites more screening patient numbers were used than patients included in the listing of patients screened, assuming sequential use of the patient screening numbers. This may indicate that some patients who were assigned screening numbers did not have any data collected for the study and/or some screening numbers may have been skipped in the assignment sequence. The sponsor's description of the enrollment of patients in this study is summarized in the following table:

Study C92-304-2: Patient Enrollment

	Number of patients (% of screened)		
	All Patients	Non-Post-MI Patients	Post-MI Patients*
Patients screened	843	7311	1120
Patients not randomized	6077 (72)	5318 (73)	759 (68)
Reasons patients not randomized[1]			
Patient not eligible	3786 (45)	3340 (46)	446 (40)
Physician refused	560 (6)	483 (7)	77 (7)
Patient refused	817 (10)	713 (10)	104 (9)
Other	1054 (13)	888 (12)	166 (15)
Not specified	82 (<1)	71 (1)	11 (<1)
Patients randomized[1]	2354 (28)	1993 (16)	361 (32)
Patients who received any study drug[2]	2181 (93)●	1849 (93%)●	332 (92)●

* Post-MI patients are patients with angina or ischemic rest pain which developed between 4 hrs and 2 weeks after an acute myocardial infarction. Non-post-MI patients are patients with a new onset of severe or accelerated angina or ischemic rest pain within the prior month, developing in the absence of an extracardiac condition.

● percent of randomized patients

sponsor's table, NDA Vol. 1.112, p. 158

As was the case in Study C92-304-1, in this study also for some reason the numbers of non-post-MI patients plus the number of post-MI patients screened and screened and not randomized in the sponsor's table do not add up to the "all patients" totals. The reason for this discrepancy is not clear. Nevertheless, it appears that about 30% of patients screened were enrolled and randomized and about 93% of patients randomized received study medication.

Two patients, one at site 12 and one at site 28, were listed as enrolled but were not randomized and did not receive study medication. Of the 2354 patients randomized, 1090 were allocated to Hirulog and 1091 to heparin. A total of 173 patients (81 Hirulog, 92 heparin) who were randomized did not receive study medication. Reasons these patients did not receive study medication were not given. Also, based on my counts using data in sponsor's data listings in NDA Vols. 1.123 p. 4 through 1.124, p. 319, there are discrepancies in the numbers of patients screened and enrolled (about 3% more patients in the data listings) as compared to the information summarized in the sponsor's table above.

Patient disposition after randomization is shown in the table below:

Study C92-304-2: Patient Disposition[2]

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Number of patients randomized	1171	1183				
Patients discontinued prior to receiving any study drug	81	92				
Patients receiving study drug	1090 (100)	1091 (100)	927 (100)	922 (100)	163 (100)	169 (100)
Discontinued due to adverse event	18 (1.7)	65 (6.0)	14 (1.5)	52 (5.6)	4 (2.5)	13 (7.7)
Discontinued due to endpoint[1]	107 (9.8)	117 (10.7)	93 (10.0)	94 (10.2)	14 (8.6)	23 (13.6)
Discontinued due to patient request	0	1 (<1)	0	1 (0.1)	0	0
Discontinued due to physician request	3 (1.2)	16 (1.5)	11 (1.2)	15 (1.6)	2 (1.2)	1 (0.6)
Other	188 (17.2)	175 (16.0)	165 (17.8)	149 (16.2)	23 (14.1)	26 (15.4)
Completed infusion per protocol	764 (70.1)	717 (65.7)	644 (69.5)	611 (66.3)	120 (73.6)	106 (62.7)

[1] Discontinuation due to an endpoint was based on investigator assessment
[2] Number of patients and in parentheses percent of patients receiving study drug.

based on sponsor's table, NDA Vol. 1.112, pp. 159 and 160 and

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Overall, about 67% of patients completed the study. About 2% of Hirulog patients and 6% of heparin patients were discontinued from the study prematurely due to adverse events. About 10% of patients in each treatment group were discontinued prematurely because of reaching a study endpoint. However, about 16% of patients discontinued prematurely because of unspecified "other" reasons.

C. **Intent-to-Treat Population:** The sponsor's Intent-to-Treat population included all 2181 patients who received study drug. The demographic features of the study population were well balanced in the overall population and in both the post-MI and non-post-MI strata. Demographic and baseline characteristics of the study population are summarized in the following table:

Study C92-304-2: Demographic and Baseline Characteristics (Intent-to-Treat Population)

Characteristic	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1090	N=1091	N=927	N=922	N=163	N=169
Age (yrs)						
mean	61.5	62.0	61.7	62.1	60.4	61.0
median	62	63	62	63	61	62
range	30-90	27-89	30-90	27-89	36-82	32-87
<65	618 (57)	609 (56)	521 (56)	508 (55)	97 (60)	101 (60)
>65	472 (43)	482 (44)	406 (44)	414 (45)	66 (40)	68 (40)
Gender						
male	733 (67)	763 (70)	620 (67)	641 (70)	113 (69)	122 (72)
female	357 (33)	328 (30)	307 (33)	281 (30)	50 (31)	47 (28)
Race						
white	1010 (93)	992 (91)	859 (93)	837 (91)	151 (93)	155 (92)
black	50 (5)	52 (5)	42 (5)	43 (5)	8 (5)	9 (5)
Hispanic	20 (2)	35 (3)	17 (2)	30 (3)	3 (2)	5 (3)
other	10 (1)	12 (1)	9 (1)	12 (1)	1 (<1)	0
Days since most recent MI						
mean	880.5	987.7	1310.5	1511.7	43.1	31.4
median	101	86	558	730	6	6
range	1-10730	0-10599	1-10730	0-10599	1-4364	0-2471
Heparin administration within 1 hr of study drug						
yes	278 (26)	260 (24)	223 (24)	202 (22)	55 (34)	58 (34)
no	812 (74)	831 (76)	704 (76)	720 (78)	108 (66)	111 (66)
Baseline ACT (sec)						
<200	998 (92)	979 (90)	847 (91)	830 (90)	151 (93)	149 (88)
200-300	56 (5)	79 (7)	49 (5)	67 (7)	7 (4)	12 (7)
>300-350	4 (<1)	4 (<1)	3 (<1)	3 (<1)	1 (<1)	1 (<1)
>350	9 (<1)	3 (<1)	6 (<1)	2 (<1)	3 (2)	1 (<1)
unknown	23 (2)	26 (2)	22 (2)	20 (2)	1 (<1)	6 (4)
Number of vessels with >50% stenosis (pre-PTCA)[1]						
1	588 (54)	590 (54)	493 (53)	495 (54)	95 (58)	95 (56)
2	335 (31)	326 (30)	289 (31)	274 (30)	46 (28)	52 (31)
3	150 (15)	170 (16)	137 (15)	148 (16)	22 (13)	22 (13)
Location of most severe lesion						
proximal RCA	511 (47)	517 (47)	432 (47)	436 (47)	79 (48)	81 (48)
mid RCA	437 (40)	458 (42)	368 (40)	386 (42)	69 (42)	72 (43)
distal RCA	113 (10)	96 (9)	102 (11)	83 (9)	11 (7)	13 (8)
Complexity of most severe lesion[2]						
A	333 (31)	381 (35)	288 (31)	337 (37)	45 (28)	44 (26)
B	599 (55)	551 (51)	523 (56)	465 (50)	76 (47)	86 (51)
C	129 (12)	139 (13)	91 (10)	103 (11)	38 (23)	36 (21)
Thrombus present in most severe lesion						
Yes	20 (2)	26 (2)	14 (2)	18 (2)	6 (4)	8 (5)
No	1041 (96)	1045 (96)	888 (96)	887 (96)	153 (94)	158 (93)
Percent stenosis in most severe lesion						
<50%	61 (6)	78 (7)	55 (6)	77 (8)	6 (4)	1 (<1)
≥50%	1000 (92)	993 (91)	847 (91)	828 (90)	153 (94)	165 (98)
TIMI grade flow in most severe lesion[3]						
0	32 (3)	32 (2)	28 (3)	21 (2)	4 (2)	5 (3)
1	13 (1)	15 (1)	10 (1)	14 (2)	3 (2)	1 (<1)
2	13 (1)	10 (<1)	10 (1)	9 (<1)	3 (2)	1 (<1)
3	1003 (92)	1019 (93)	854 (92)	860 (93)	149 (91)	159 (94)
Previous cardiovascular disease:						
prior coronary angioplasty	319 (29)	283 (26)	304 (33)	273 (30)	15 (9)	10 (6)
prior coronary bypass surgery	103 (9)	123 (11)	97 (10)	111 (12)	6 (4)	12 (7)
myocardial infarction	487 (45)	477 (44)	333 (36)	317 (34)	154 (94)	160 (95)
Patients with angina						
New onset of severe or accelerated angina; no rest pain	436 (40)	388 (36)	398 (43)	347 (38)	38 (23)	41 (24)
Angina at rest within part month	655 (60)	700 (64)	528 (57)	537 (62)	127 (78)	127 (75)

[1] Fewer than 1% of patients had >50% Left main coronary artery stenosis (pre-PTCA)
[2] Complexity of most severe lesion was determined by the [redacted] using protocol definitions where complexity A<B<C
[3] TIMI grade flow was determined by the [redacted] where 0=no perfusion; 1=penetration without perfusion; 2=partial perfusion; 3=complete perfusion

from sponsor's tables, NDA Vol. 1.112, pp. 167 through 186

With regard to baseline cardiovascular features, the treatment groups were well-balanced in all regards with the exception of percent stenosis in the most severe lesion where in the post-MI patient group there were somewhat more patients with ≥50% stenosis (98% vs. 94%, p=0.044). In the non-post-MI group 91.4% of Hirulog patients and 89.8% of heparin patients had ≥50% stenosis (p=0.049).

Most patients had one or more coronary risk factors. The prevalence of these risk factors and of other cardiovascular conditions and diseases in this study population and the two strata was essentially identical to that in study C92-304-1. About 54% of all patients had history of hypertension and 25% were current cigarette smokers. Forty-six percent had elevated cholesterol requiring treatment and 21% had diabetes mellitus. Smoking was more common in the post-MI group (about 38% of patients). Fewer than 6% of patients had history of congestive heart failure, valvular heart disease, significant ventricular arrhythmias, cerebral vascular accident, or transient ischemic attack. About 20% of patients had history of "other cardiac conditions" which consisted chiefly of cardiac dysrhythmias, ill-defined heart disease, conduction disorders, cardiovascular system symptoms, abnormal function study, other heart/pericardial surgery, surgery on heart vessels, and "other endocardial disease". More than 80% of all patients had Canadian Cardiovascular Society Classification of Class III or IV.

D. **Evaluable Population:** One hundred sixty-three patients who received study medication were excluded from the evaluable population. These included 138 non-post-MI patients (65 Hirulog; 73 heparin) and 25 post-MI patients (10 Hirulog; 15 heparin). These patients and reasons for exclusion are summarized in the following table:

Study C92-304-2: Patients Excluded from the Evaluable Population

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Total patients randomized who received study medication	1090	1091	927	922	163	169
Total patients excluded from evaluable population:	75[c]	88[d]	65[c]	73[d]	10[c]	15
Angioplasty catheter not inflated	31	32	29	26	2	6
Atherectomy or laser device utilized	6	10	4	8	2	2
Saphenous vein grafts >3yrs old[a]	3	3	2	2	1	1
Not a candidate for PTCA	1	0	1	0	0	0
Did not have unstable angina	2	3	0	1	2	2
Saphenous vein grafts >3yrs old treated[b]	35	45	30	41	5	4

[a] Patient had saphenous vein grafts over 3 yrs old, aorto-ostial lesions, or diffuse lesions >20mm in length.
[b] Patient had saphenous vein grafts over 3 yrs old, aorto-ostial lesions, or diffuse lesions >20mm in length treated.

[c] One patient (#010/0008, post-MI), a 71yo man did not have unstable angina and did not have angioplasty catheter inflated; two patients (#034/0009, post-MI), a 67yo man, and (#054/0532, non-post-MI), a 55 yo man had saphenous vein grafts over 3 yrs old treated with atherectomy or laser device.
[d] Three patients (#001/0522, non-post-MI), a 49yo woman, (#012/527, non-post-MI), a 68yo man, and (#012/0537, non-post-MI), a 45yo man, had saphenous vein graft over 3 yrs old treated and did not have angioplasty catheter inflated; one patient (#034/0617, non-post-MI), a 78yo man, had saphenous vein graft over 3 yrs old treated with atherectomy or laser device; one patient (#060/0595, non-post-MI), an 87yo woman, had saphenous vein grafts over 3 yrs old and had saphenous vein grafts over 3 yrs old treated.

reviewer's original table, based on data in sponsor's table, NDA Vol. 1.117 pp. 428 through 441

For the evaluable cohort, in the overall population and among the non-post-MI patients there was an imbalance between treatment groups in complexity of most severe lesion with the heparin group having less complex lesions (all patients: 37% A lesions and 51% B lesions in the heparin group vs. 32% A lesions and 56% B lesions in the Hirulog group, p=0.046; non-post-MI patients: 39% A lesions and 51% B lesions in the heparin group vs. 32% A lesions and 57% B lesions in the Hirulog group, p=0.027). Also, among post-MI patients fewer heparin patients than Hirulog patients had <50% stenosis in the most severe lesion (<1% vs. 4%, p=0.050), while among non-post-MI patients, fewer Hirulog patients than heparin patients had <50% stenosis in the most severe lesion (6% vs. 8%, p=0.045).

Patients in whom angioplasty was unsuccessful (AVC) were The National Heart, Lung and Blood Institute defines abrupt vessel closure (AVC) as occlusion of dilated lesion or adjacent segment, occurring either in the catheterization laboratory or during post-PTCA hospitalization within 24 hours after PTCA.

E. **Efficacy Analysis:** Among the 2181 patients who were randomized and received study medication, 235 patients (111 Hirulog, 124 heparin) suffered major events (death, MI, revascularization, established AVC or impending AVC) during hospitalization (based on sponsor's data listing NDA Vol. 1.131, pp. 52 through 149). Most events were in the non-post-MI population. In the post-MI population, 15 Hirulog patients and 28 heparin patients experienced major events. The efficacy results for the total population and for the non-post-MI and the post-MI populations are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Study C92-304-2: Incidence of Procedural Failure During Hospitalization (Intent-to-Treat Population)

Event	All Patients			Non-Post-MI Patients			Post-MI Patients		
	Hirulog	Heparin	p-value	Hirulog	Heparin	p-value	Hirulog	Heparin	p-value
Total number of patients	1090	1091		927	922		163	169	
Overall procedural failure	83 (8)	87 (8)	0.796	74 (8)	65 (7)	0.431	9 (6)	22 (13)	0.018*
Death, MI or revascularization	62 (6)	72 (7)	0.407	57 (6)	51 (6)	0.552	5 (3)	21 (12)	0.001*
Death or MI	27 (2)	28 (3)	0.922	25 (3)	19 (2)	0.358	2 (1)	9 (5)	0.029*
Death	6 (<1)	5 (<1)	0.680	6[a] (<1)	3[b] (<1)	0.229	0	2[c] (1)	0.039*
Documented MI not present at enrollment	23 (2)	24 (2)	0.891	21 (2)	17 (2)	0.527	2 (1)	7 (4)	0.085
Revascularization	47 (4)	54 (5)	0.335	43 (5)	43 (5)	0.989	4 (2)	14 (8)	0.017*
Established AVC	23 (2)	24 (2)	0.936	20 (2)	21 (2)	0.896	3 (2)	3 (2)	0.979
Impending AVC	11 (1)	2 (<1)	0.009**	9 (<1)	2 (<1)	0.028*	2 (1)	0	0.082

* Significant at 0.050 level; **significant at 0.010 level.

[1] p-value is from the likelihood ratio test for treatment based on a logistic regression model with covariates for site, post-MI group, age (<65, >65), multivessel disease, preprocedural % stenosis, and treatment.

[2] Revascularization = clinical deterioration of cardiac origin requiring revascularization. Note: MI was determined by [redacted] using protocol-specified criteria.

Note: AVC was determined by [redacted] using protocol-specified criteria.

Note: Percentages are relative to the total number of patients in each treatment group.

[a] Description of non-post MI deaths:

sponsor's table, NDA Vol. 1.112, p.187

APPEARS THIS WAY
ON ORIGINAL

Overall procedural failure was defined as the occurrence of any one of the components of procedural failure. (Patients suffering more than one component were counted only once). There was no significant difference between treatment groups in the proportions of patients suffering procedural failure. In the non-post-MI stratum, numerically more Hirulog patients suffered overall procedural failure than did heparin patients (74/927 vs. 65/922). In the post-MI patient stratum the overall procedural failure rate was significantly less in the Hirulog group as compared to the heparin group (6% vs. 13%); however, these figures represent a relatively small number of events (9/163 patients with events in the Hirulog group and 22/169 patients with events in the heparin group).

Death was determined by the individual investigator at that site. The death rates in this study were very low (fewer than 1% of patients with in hospital death). Overall there were no differences between treatment groups in proportions of deaths. In the non-post-MI stratum, numerically more Hirulog patients died than in the heparin group (6/927 vs. 3/922). In the post-MI stratum the sponsor found a statistically significant difference in deaths between treatment groups with 0/163 Hirulog patients and 2/169 heparin patients dying ($p=0.039$).

Clinical deterioration of cardiac origin requiring revascularization was determined by the investigator and specified on the CRF. In the overall population and in the non-post-MI population there were no statistically significant differences between treatment groups in the incidence of required revascularizations. However, in the post-MI stratum, significantly more heparin patients than Hirulog patients required revascularization (14/169 heparin patients vs. 4/163 Hirulog patients, $p=0.017$).

Myocardial infarction (MI) not present at enrollment, identified by the [redacted] was defined as defined as any of the following: definite Q-wave MI, definite non-Q-wave MI, and definite MI with new LBBB. Established and impending AVC were identified by the [redacted] There were no statistically significant differences between treatment groups in the proportions of patients having documented MI nct present at enrollment, established AVC or Impending AVC.

Results of efficacy analyses for the Evaluable population were similar to those for the intent-to-treat population. Sponsor's results for the evaluable population are attached to this review as Appendix G. The sponsor's analyses used adjudicated data (clinical endpoints confirmed according to the protocol definitions by a Morbidity and Mortality Classification Committee (MMCC), which consisted of 5 principal investigators from participating clinical sites). Procedure failure rates and incidence of MI were higher in the investigators' assessments than in the adjudicated data. For example in the overall population, in the Hirulog group the proportion of procedure failures using the investigators' assessments was 110/1090 (10%) for Hirulog and 125/1091 (11%) for heparin. Results of analyses based on investigators assessments were similar to those obtained using the adjudicated data.

For abrupt vessel closure (AVC) the data analyzed was only that associated with the initial PTCA procedure and confirmed by the [redacted] AVC occurring subsequent to the initial PTCA were likely collected in association with a clinical event and hence were not included as AVC events. Thus, according to the [redacted] reviewed data there were 23 Hirulog patients and 24 heparin patients with established AVC and 11 Hirulog patients and 2 heparin patients with impending AVC. However, based on the data included in the

sponsor's listing of Major Events During Hospitalization (NDA Vol. 1.131, pp. 52 through 149) there were 40 Hirulog patients and 27 heparin patients with established AVC and 48 Hirulog patients and 56 heparin patients with impending AVC.

Multiple comparisons were not taken into account in any of these comparisons of the treatment groups.

During hospitalization there were 6 deaths of patients on Hirulog and 5 deaths of patients on heparin. The most frequent event was impending abrupt vessel closure (IAVC) which occurred in 48 patients on Hirulog and 56 patients on heparin. An additional 40 Hirulog patients and 27 heparin patients experienced established vessel closure.

Details of study drug administration and use of heparin prior to study drug are summarized in the following table:

Study C92-304-2: Summary of Study Drug Administration (Intent-to-Treat Population)[1]

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
No. of Patients receiving bolus #1	1090 (100)	1091 (100)	927 (100)	922 (100)	163 (100)	169 (100)
No. of Patients receiving bolus #2	567 (52)	350 (32)	472 (51)	281 (30)	95 (58)	69 (41)
No. of patients receiving bolus #3	268 (24)	113 (10)	216 (23)	92 (10)	50 (31)	21 (12)
Duration of study drug administration (hrs)						
mean	16.24	15.8	16.26	15.86	16.14	15.51
median	18.3	18.2	18.3	18.3	18.7	18.2
range	0-27	0.1-25.6	0-27	0.1-25.6	0.4-24.6	0.1-25.0
Total amount of study drug administered (mg/kg [Hirulog] or units/kg [heparin])						
mean	12.71	433.25	12.71	432.37	12.66	438.03
median	13.9	456.8	13.9	455.0	13.9	476.0
range						
Number of patients administered heparin prior to start of study drug	610 (60)	657 (66)	479 (56)	520 (61)	131 (86)	137 (89)
Time since last heparin administration prior to start of study drug, number of patients						
≤1 hr	245 (23)	239 (21)	193 (21)	186 (21)	52 (32)	53 (31)
>1-6hrs	337 (31)	402 (37)	263 (28)	318 (34)	74 (45)	84 (50)
>6hrs	71 (8)	79 (8)	58 (7)	64 (7)	13 (8)	14 (8)
Duration of heparin administration prior to start of study drug (hrs)						
0-12 hrs	135 (12)	145 (13)	117 (13)	128 (14)	18 (11)	17 (10)
>12-24hrs	217 (20)	233 (21)	172 (19)	187 (20)	45 (28)	46 (27)
>24 hrs	272 (25)	316 (29)	204 (22)	237 (26)	68 (42)	79 (47)

[1] Numbers in parentheses are percent of patients. Percentages are relative to the total number of patients in each treatment group.

from sponsor's tables, NDA Vol. 1.112, pp. 218 through 228

More Hirulog than heparin patients received second and third boluses of study medication (for patients randomized to Hirulog, second and third boluses were placebo).

About 6% of patients received heparin via some route after discontinuation of study drug.

About 6% of patients (66 Hirulog; 74 heparin) had major protocol violations. These protocol violations are summarized in the table below:

Study C92-304-2: Protocol Violations

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Total patients randomized	1090	1091	927	922	163	169
Protocol violations:						
Aspirin not taken day of study drug administration	5*	4	5*	3	0	1
Excluded medication taken	33*	31	28*	27	5	4
Heparin administration within 30 min prior to study drug	10	16	7	14	3	2
Patient misrandomized	19	23	8	8	11	15

* One patient (#114-0508) had two protocol violations: did not take aspirin on day study drug was administered and took excluded medication (Ticlopidine).

reviewer's original table, based on data in sponsor's table, NDA Vol. 1.112, pp. 161 through 165

For assessing influence of investigative center on the study results, the study sites were grouped geographically into three "sites". The grouping of centers in summarized in the table below:

Pooled Site	Formed by Pooling Sites in:	Number of Patients Randomized / Treated
1	California, Colorado, Minnesota, Missouri, Nebraska, Oklahoma, Texas, Utah, Wisconsin, Arizona, Iowa, New Mexico, Wyoming, Canada and Europe	748 / 682
2	Connecticut, Washington D.C., Illinois, Indiana, Massachusetts, Maryland, Maine, Michigan, New Hampshire, New York, Ohio, Pennsylvania, Delaware, New Jersey, and Rhode Island	1078 / 1005
3	Alabama, Florida, Georgia, North Carolina, Virginia, Kentucky, and Tennessee	528 / 494

sponsor's table, NDA Vol. 1.117, p. 393

There were no statistically significant differences among the geographic areas in the study results.

E. **Six-Month Follow-up:** Follow-up data was available for about 95% of all patients who received any study drug in this study. The follow-up data are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Study C92-304-1: Incidence of Clinical Events at 6-Month Follow-up (Intent-to-Treat Population)

Event	All Patients			Non-Post-MI Patients			Post-MI Patients		
	Hirulog	Heparin	p-value	Hirulog	Heparin	p-value	Hirulog	Heparin	p-value
Total number of patients	1090	1091		927	922		163	169	
Total number of patients with 6-month follow-up data	1033 (95)	1033 (95)	N.D.	882 (95)	869 (94)	N.D.	151 (93)	164 (97)	N.D.
Any Event	532 (52)	507 (49)		451 (51)	437 (50)		81 (54)	70 (43)	
Death, MI or revascularization	218 (21)	216 (21)		187 (21)	185 (21)		31 (21)	33 (20)	
Death or MI	46 (4)	36 (3)		34 (4)	28 (3)		11 (7)	7 (4)	
Death	20 (2)	15 (1)		15 (2)	12 (1)		5 (3)	3 (2)	
MI	29 (3)	22 (2)		23 (3)	17 (2)		6 (4)	5 (3)	
Revascularization	193 (19)	201 (19)		168 (19)	171 (20)		25 (17)	30 (18)	
PTCA	137 (13)	150 (15)		119 (13)	126 (14)		18 (12)	24 (15)	
CABG	80 (8)	71 (7)		71 (8)	61 (7)		9 (6)	10 (6)	
Angina requiring hospitalization	248 (24)	236 (23)		216 (24)	207 (24)		32 (21)	29 (18)	
Angina	492 (48)	465 (45)		422 (48)	400 (46)		70 (46)	65 (40)	
Coronary angiography	257 (25)	271 (26)		220 (25)	237 (27)		37 (25)	34 (21)	

Note: Percentages are relative to the total number of patients in each treatment group.
N.D. = not determined

sponsor's table, modified, NDA Vol. 1.112, p. 207

Differences between treatment groups were even less apparent at 6-month follow-up than immediately following PTCA. Among all patients there was a trend toward more deaths and myocardial infarctions in the Hirulog group. In the post-MI population there was a trend toward more events in the Hirulog patients as compared to the heparin patients at 6 months. No formal statistical comparisons were made of this data.

F. **Safety Analysis:** As for Study C92-304-1, for this study the sponsor has summarized and analyzed the incidence of "treatment-emergent" events, defined as those events that occurred or worsened following the administration of study drug. Events were separated into bleeding events and non-bleeding adverse events. Analyses were done only of serious adverse events, all bleeding events and major and minor bleeding events. The incidences of these events are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Study C92-304-2: Summary of Bleeding Events[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1090	N=1091	N=927	N=922	N=163	N=169
Any Bleeding Event	561 (51)	835 (77)	483 (52)	720 (78)	78 (48)	115 (68)
Any Bleeding Events Seen in ≥1% of Patients in Any Group:						
Puncture site hemorrhage	210 (19)	528 (48)	187 (20)	453 (49)	23 (14)	75 (44)
Cath. site ecchymosis without hematoma	177 (16)	245 (22)	150 (16)	213 (23)	27 (17)	32 (19)
Cath. site hematoma	160 (15)	340 (31)	140 (15)	301 (33)	20 (12)	39 (23)
Hematuria	157 (14)	216 (20)	132 (14)	189 (20)	25 (15)	27 (16)
Ecchymosis	84 (8)	164 (15)	73 (8)	142 (15)	11 (7)	22 (13)
Groin hematoma	15 (1)	19 (2)	13 (1)	16 (2)	2 (1)	3 (2)
Anemia	13 (1)	23 (2)	13 (1)	16 (2)	0	7 (4)
Venipuncture site prolonged bleeding	11 (1)	26 (2)	7 (<1)	24 (3)	4 (2)	2 (1)
Other	10 (<1)	25 (2)	10 (1)	22 (2)	0	3 (2)
Other hematoma	9 (<1)	20 (2)	7 (<1)	16 (2)	2 (1)	4 (2)
CABG/Op	8 (<1)	11 (1)	8 (<1)	9 (<1)	0	2 (1)
Hemoptysis	8 (<1)	13 (1)	8 (<1)	10 (1)	0	3 (2)
Hematemesis	6 (<1)	27 (2)	5 (<1)	23 (2)	1 (<1)	4 (2)
Epistaxsis	5 (<1)	11 (1)	5 (<1)	10 (1)	0	1 (<1)
Bloody chest tube drainage	4 (<1)	7 (<1)	4 (<1)	5 (<1)	0	2 (1)
Gastrointestinal hemorrhage	3 (<1)	3 (<1	3 (<1)	1 (<1)	0	2 (1)
Any Major Bleeding Event	32 (3)	86 (8)	31 (3)	67 (7)	1 (<1)	19 (11)
Major Bleeding Events:						
Puncture site hemorrhage	13 (1)	22 (2)	12 (1)	17 (2)	1 (<1)	5 (3)
Catheterization site hematoma	6 (<1)	38 (3)	8 (<1)	28 (3)	0	10 (6)
Anemia	5 (<1)	16 (1)	5 (<1)	11 (1)	0	5 (3)
Pseudo aneurysm	5 (<1)	2 (<1)	5 (<1)	2 (<1)	0	0
CABG/Op	3 (<1)	8 (<1)	3 (<1)	6 (<1)	0	2 (1)
Catheterization site ecchymosis without hematoma	3 (<1)	2 (<1)	3 (<1)	2 (<1)	0	0
Ecchymosis	3 (<1)	9 (<1)	3 (<1)	8 (<1)	0	1 (<1)
Retroperitoneal bleeding	3 (<1)	8 (<1)	3 (<1)	8 (<1)	0	0
Blood in stool	2 (<1)	1 (<1)	2 (<1)	1 (<1)	0	0
Groin hematoma	2 (<1)	6 (<1)	2 (<1)	4 (<1)	0	2 (1)
Injection site hematoma	2 (<1)	0	2 (<1)	0	0	0
Hematuria	1 (<1)	8 (<1)	1 (<1)	8 (<1)	0	0
Other hematoma	1 (<1)	3 (<1)	1 (<1)	2 (<1)	0	1 (<1)
Hematemesis	0 (<1)	3 (<1)	0	3 (<1)	0	0
Venipuncture site prolonged bleeding	0 (<1)	3 (<1)	0	2 (<1)	0	1 (<1)
Other major bleed[b]	8 (<1)	9 (<1)	8 (<1)	7 (<1)	0	2 (<1)
Any Major Bleeding Event Associated with Hemoglobin Decrease of >3g/dL	16 (1)	58 (5)	16 (2)	42 (5)	0	16 (9)
Any Major Bleeding Event Associated with Transfusion	19 (2)	48 (4)	19 (2)	37 (4)	0	11 (7)
Premature Discontinuations Due to Bleeding Events	7 (<1)	57 (5)	7 (<1)	46 (5)	0	11 (7)
Dose Reduction Due to Bleeding Events	19 (2)	73 (7)	17 (2)	70 (8)	2 (1)	3 (2)

[a] Numbers are numbers of patients with percent of patients in parentheses

[b] Other major bleeds included: in the Hirulog group, one case each of bloody chest tube drainage, coagulation disorder, hemopericardium, hemoptysis, hemothorax, and lung hemorrhage; in the heparin group one case each of coronary perforation, epistaxsis, gastrointestinal hemorrhage, unspecified hemorrhage, intra-abdominal bleeding, melena, and thrombocytopenia; and in each (Hirulog and heparin) treatment group, one case of pericardial effusion and one case of unspecified major bleeding.

reviewer's original table, based on sponsor's tables, NDA Vol. 1.112, pp. 299 through 351 and 369 through 378 and 392

Fifty-one percent of Hirulog patients and 77% of heparin patients experienced some bleeding after the start of study drug administration. Treatment-emergent major bleeding events occurred in 32 Hirulog patients (3%) and 86 heparin patients (8%). The percentages of post-MI patients experiencing these events were somewhat less in the post-MI patients Hirulog patients and greater in the post-MI heparin patients as compared to the overall population (<1% of Hirulog patients and 11% of heparin patients). The most frequent events were puncture site hemorrhage, catheterization site hematoma (especially in the heparin group) and anemia. About 50-59% of patients in the Hirulog group and 56-67% of patients in the heparin group who experienced major bleeding had a hemoglobin decrease of $\geq$3g/dL and/or required transfusion. Among patients with bleeding events, the median time to first occurrence of any bleeding event was significantly longer ($p=0.001$) in the Hirulog group as compared to the heparin group (19.5 hrs vs. 8.3 hrs). Time to event (life table analysis) results were similar for major bleeding and minor bleeding and for non-post MI patients and post-MI patients except for post-MI patients having major bleeding events (where there was only one major bleeding event in the Hirulog group and that event occurred at 1.8 hrs after initiation of the infusion). Most of the bleeding events in both treatment groups and for non-post-MI and post-MI patients were felt by the investigator to be possibly, probably or definitely study drug related.

Sixteen Hirulog patients and 41 heparin patients had bleeding events that were classified as serious (death, life-threatening, caused or prolonged hospitalization, or caused a permanent disability). Seven Hirulog patients and 57 heparin patients were discontinued from the study prematurely due to bleeding events and 19 Hirulog patients and 73 heparin patients had study drug dose reduced due to bleeding events. Four heparin patients had study drug temporarily discontinued due to bleeding events. No Hirulog patients had study drug temporarily discontinued.

Higher ACT values were associated with a greater incidence of bleeding events in both treatment groups in both non-post-MI and post-MI patients. For patients with ACT values >300, the incidence of all bleeds and major bleeds consistently tended to be greater in the heparin group than in the Hirulog group for non-post-MI and post-MI patients. Incidence of bleeding adverse events as related to ACT values is summarized in the following table:

Study C92-304-2: Numbers of Patients with Bleeding Events in Relation to ACT Values (Intent-to-Treat Population)*

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1090	N=1091	N=927	N=922	N=163	N=169
Any Bleeding Event	561/1090 (51)	835/1091 (77)	483/927 (52)	720/922 (78)	78/163 (48)	115/169 (68)
Any Bleeding Event within 24 hrs	457/1090 (42)	763/1091 (70)	397/927 (43)	658/922 (71)	60/163 (37)	105/169 (62)
For All Patients with Bleeding Events within 24Hrs: Bleeding with ACT Values:						
≤200	5/9 (56)	9/16 (56)	4/8 (50)	7/14 (50)	1/1 (100)	2/2 (100)
200 - 300	84/219 (38)	45/69 (65)	70/178 (39)	37/54 (69)	14/41 (34)	8/15 (53)
>300 - 350	128/329 (39)	145/212 (68)	108/275 (39)	121/174 (70)	20/54 (37)	24/38 (63)
>350	236/524 (45)	562/787 (71)	211/457 (46)	491/673 (73)	25/67 (37)	71/114 (62)
Bleeding Events without ACT Values	4/9 (44)	2/7 (29)	4/9 (44)	2/7 (29)	0/0 (0)	0/0 (0)
Any Major Bleeding Event	32/1090 (3)	86/1091 (8)	31/927 (3)	67/922 (7)	1/163 (<1)	19/169 (11)
Any Major Bleeding Event within 24 hrs	17/1090 (2)	72/1091 (7)	16/927 (2)	56/922 (6)	1/163 (<1)	16/169 (9)
For All Patients with Major Bleeding Events within 24Hrs: Major Bleeding with ACT Values:						
<200	0/9 (0)	1/16 (6)	0/8 (0)	0/14 (0)	0/1 (0)	1/2 (50)
200 - 300	4/219 (2)	5/69 (7)	4/178 (2)	3/54 (6)	0/41 (0)	2/15 (13)
>300 - 350	3/329 (<1)	14/212 (7)	3/275 (1)	13/174 (7)	0/54 (0)	1/38 (3)
>350	9/524 (2)	52/787 (7)	8/457 (2)	40/673 (6)	1/67 (<1)	12/114 (11)
Major Bleeding Events without ACT Values	1/9 (11)	0/7 (0)	1/9 (11)	0/7 (0)	0/0 (0)	0/0 (0)

* numbers given are number of patients and (in parentheses) percent of patients evaluated

reviewer's original table, based on sponsor's tables, NDA Vol. 1.112 pp. 333 through 341

Kaplan-Meyer survival curves of bleeding as a function of time showed a statistically significantly lower event rate for Hirulog as compared to heparin (p-value ≤0.001) over the 48 hours after start of study drug. Median time to occurrence of any event was 19.5 hrs for Hirulog and 8.3 hrs for heparin. Results were similar for post-MI and non-post-MI patients.

In this study 892/1090 (82%) of patients treated with Hirulog and 904/1091 (83%) of patients treated with heparin reported one or more adverse events. As in Study C92-304-1, the most frequent adverse events were back pain, pain, headache, injection site pain, hypotension, and nausea. Thrombocytopenia was listed as an adverse event for 1 Hirulog patient and 1 heparin patient. Adverse events occurring in 5% or more of the patients in any treatment group are summarized by body system in the table below:

Study C92-304-2: Summary by Body System of Adverse Occurring in ≥5% of Patients in Any Group[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1090	N=1091	N=927	N=922	N=163	N=169
Any Adverse Event	892 (82)	904 (83)	761 (82)	771 (84)	131 (80)	133 (79)
Body As A Whole	705 (65)	727 (67)	601 (65)	621 (67)	104 (64)	106 (63)
Pain back	470 (43)	474 (43)	399 (43)	403 (44)	71 (44)	71 (42)
Pain	169 (16)	176 (16)	135 (15)	152 (16)	34 (21)	24 (14)
Headache	132 (12)	102 (9)	107 (12)	90 (10)	25 (15)	12 (7)
Injection site pain	88 (8)	127 (12)	79 (9)	110 (12)	9 (6)	17 (10)
Pain pelvic	74 (7)	95 (9)	67 (7)	78 (8)	7 (4)	17 (10)
Pain abdominal	53 (5)	49 (4)	46 (5)	44 (5)	7 (4)	5 (3)
Fever	48 (4)	49 (4)	41 (4)	37 (4)	7 (4)	12 (7)
Cardiovascular System	298 (27)	358 (33)	260 (28)	310 (34)	38 (23)	48 (28)
Hypotension	125 (11)	191 (18)	110 (12)	171 (19)	15 (9)	20 (12)
Hypertension	62 (6)	59 (5)	56 (6)	54 (6)	6 (4)	5 (3)
Bradycardia	56 (5)	80 (7)	49 (5)	75 (8)	7 (4)	5 (3)
Digestive System	240 (22)	260 (24)	205 (22)	235 (25)	35 (21)	25 (15)
Nausea	151 (14)	177 (16)	132 (14)	162 (18)	19 (12)	15 (9)
Vomiting	66 (6)	82 (8)	59 (6)	76 (8)	7 (4)	6 (4)
Dyspepsia	45 (4)	51 (5)	39 (4)	47 (5)	6 (4)	4 (2)
Metabolic and Nutritional Disorders	79 (7)	86 (8)	69 (7)	75 (8)	10 (6)	11 (7)
Nervous System	278 (26)	250 (23)	238 (26)	216 (23)	40 (25)	34 (20)
Anxiety	77 (7)	67 (6)	66 (7)	61 (7)	11 (7)	6 (4)
Insomnia	73 (7)	68 (6)	65 (7)	62 (7)	8 (5)	6 (4)
Nervousness	62 (6)	46 (4)	55 (6)	37 (4)	7 (4)	9 (5)
Respiratory System	93 (9)	76 (7)	81 (9)	64 (7)	12 (7)	12 (7)
Skin	49 (4)	42 (4)	39 (4)	32 (3)	10 (6)	10 (6)
Urogenital System	90 (8)	76 (7)	80 (9)	69 (7)	10 (6)	7 (4)
Urinary retention	50 (5)	44 (4)	44 (5)	41 (4)	6 (4)	3 (2)

[a] Numbers are numbers of patients with percent of patients in parentheses

reviewer's original table, based on sponsor's table, NDA Vol. 1.112, pp. 371 through 379

Most of the reported adverse events were not serious and most of the serious events involved bleeding. Bleeding events are discussed above. Fourteen patients in the Hirulog group and 19 patients in the heparin group experienced other (non-bleeding) serious adverse events. These serious events are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Study C92-304-2: Summary of Serious Non-Bleeding Adverse Events[a] (Intent-to-Treat Population)

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
	N=1090	N=1091	N=927	N=922	N=163	N=169
Any Serious Non-Bleeding Adverse Event	14 (1)	19 (2)	13 (1)	15 (2)	1 (<1)	4 (2)
Serious Non-Bleeding Events Reported in ≥2 Patients in Any Treatment Group:						
Infection	2 (<1)	0	2 (<1)	0	0	0
Hypotension	3 (<1)	1 (<1)	3 (<1)	1 (<1)	0	0
Vascular anomaly	2 (<1)	0	1 (<1)	0	1 (<1)	0
Heart arrest	0	2 (<1)	0	1 (<1)	0	1 (<1)
Ventricular fibrillation	0	2 (<1)	0	2 (<1)	0	0
Anemia	0	2 (<1)	0	2 (<1)	0	0
Cerebral ischemia	1 (<1)	4 (<1)	1 (<1)	2 (<1)	0	2 (<1)
Kidney failure	3 (<1)	1 (<1)	3 (<1)	1 (<1)	0	0
Oliguria	2 (<1)	0	2 (<1)	0	0	0

[a] Numbers are numbers of patients with percent of patients in parentheses

reviewer's original table, based on sponsor's table, NDA Vol. 1.112, pp. 430 through 431

Non-bleeding serious adverse events were infrequent and no clear trends for these events for Hirulog vs. heparin were apparent.

Six patients randomized to Hirulog and 5 patients randomized to heparin died during hospitalization. The 6 Hirulog patients who died in hospital were as follows:

- Patient #005/0529 was a 76 year old white woman with hypertension who received Hirulog bolus and 1 placebo bolus and Hirulog infusion for about 1 hour. During PTCA she became hypotensive, bradycardic, and developed respiratory distress. She was discontinued from the study and had emergency CABG and intra-arterial balloon pump placement. She developed pericardial hemorrhage, severe coagulopathy, irreversible shock and multisystem failure and died. Events were judged possibly related to study drug.

- Patient #009/0520 was a 60 year old white man with hypertension and S/P MI x 2 who was hospitalized with unstable angina to undergo PTCA. He received Hirulog bolus and 1 placebo bolus and infusion for about 1 hr. PTCA was successful but an established abrupt vessel closure was found after completion and the patient was withdrawn from the study. Repeat PTCA was successful but patient developed adult respiratory distress syndrome and subsequently died about 7 weeks later.

- Patient #028/0650 was a 74 year old white man with history of hypertension and MI hospitalized for PTCA treatment of unstable angina. He received bolus of Hirulog and 1 placebo bolus and Hirulog infusion. During PTCA impending abrupt vessel closure was detected and patient was discontinued from the study. The patient underwent coronary stent placement but died several days later due to cardiogenic shock and cardiac arrest judged unrelated to study drug.

- Patient #034/0553 was an 82 year old white woman with history of hypertension, elevated cholesterol, insulin-dependent diabetes mellitus and myocardial infarction. She was hospitalized for unstable angina. She was entered into the study and received Hirulog bolus and infusion for 17 hrs. PTCA was successful. She had multiple concurrent medications including insulin, lasix, prednisone and Septra, among others. She had elevated renal function laboratory tests during study (baseline values not available). Patient died about 2 weeks after study entry due to renal failure and urosepsis judged to be unrelated to study drug.

- Patient #044/0544 was a 79 year old white woman with history of hypertension, congestive heart failure, valvular heart disease, and diabetes. She was hospitalized with unstable angina. She received Hirulog bolus and infusion. (She also had multiple concurrent medications including lisinopril, Cardizem, Lasix, and heparin, among others. Impending abrupt vessel closure was detected during PTCA and she was withdrawn from the study. Coronary stents were placed, but patient developed pulmonary edema with severe respiratory compromise and died. Death was judged unrelated to study drug.

- Patient #050/0502 was a 79 year old white woman with history of elevated cholesterol. She was hospitalized for PTCA due to unstable angina. She received Hirulog bolus and infusion for about 3 hours. During the procedure she had an unfavorable dissection with concomitant acute occlusion. She was withdrawn from the study and no other procedures were done. Six days later she developed sudden onset chest pain, pulmonary edema and shock and died. Events were judged unrelated to study drug.

The 5 heparin patients who died in hospital were as follows:

- Patient #012/0516 was an 85 year old white woman with history of hypertension, congestive heart failure, elevated cholesterol, diabetes mellitus, and MI about 2 months prior to study. She received heparin bolus but became hemodynamically unstable 10 minutes after start of heparin infusion. She was withdrawn from the study and an intra-aortic balloon pump was placed. She underwent CABG. She had several unspecified hemorrhages requiring transfusion. She died 4 days after study entry. Hemodynamic instability was judged unrelated to study drug.

- Patient #028/0513 was a 70 year old white man with no prior cardiac history who had unstable angina. He was randomized and received heparin bolus and infusion and aspirin. Patient developed severe back pain and hypotension after about 1 hr of infusion and he was withdrawn from the study. Abdominal ultrasound suggested aortic dissection and the abdominal CT showed a large retroperitoneal hemorrhage. Five days after hospitalization he died of myocardial infarction and cardiogenic shock judged to be unrelated to study drug.

- Patient #034/0001 was a 77 year old white man with hypertension and history of MI who entered the study and underwent PTCA for treatment of post-infarction angina. He received heparin bolus and infusion (17 hrs) without problem. About 29 hrs after discontinuation of study drug he suffered an embolic cerebrovascular accident and died. The death was judged unrelated to study drug.

- Patient #044/0013 was a 72 year old Hispanic woman with hypertension who was hospitalized for PTCA treatment of post-infarction angina. She received heparin bolus and infusion. During PTCA she developed impending abrupt vessel closure. She was withdrawn from the study and underwent an unsuccessful attempt at stent placement and then had CABG surgery. She did not do well and died due to ventricular failure and electromechanical dissociation felt to be unrelated to study drug.

- Patient #052/0006 was a 56 year old white woman with hypertension hospitalized for PTCA treatment of post-infarction angina. She received heparin bolus and infusion for 6 hrs and then developed a fever (judged probably study drug related). She was withdrawn from the study. She suffered severe cerebral ischemia and neuropathy, bleeding from puncture sites, some vomiting and hypotonia. She died 3 days after study entry due to cerebral vascular accident with secondary herniation.

An additional 14 patients in the Hirulog group and an additional 10 patients in the heparin group died during the 6-month follow-up period. Causes of death were given as: myocardial infarction, 5 (1 peri-operative); respiratory failure (chronic obstructive pulmonary disease; pneumonia), 1; multiple organ failure, 1; natural causes, 1; congestive heart failure, 1; unknown or unavailable, 4; "fell over dead after lunch", 1.

With regard to clinical laboratory studies, there was less of a shift to lower values of hemoglobin, hematocrit, and RBC consistent with less bleeding in the Hirulog group. Also, ACT values during treatment with study drug tended to be lower in the Hirulog group as compared to the heparin group. Shifts from low/normal to high SGOT values were somewhat more frequent in the Hirulog group (104/846 patients, 12.3%) as compared to the heparin group (72/828, 8.7%).

Incidence of clinically significant low platelet counts ($<120x10_3$/uL) was similar in Hirulog patients (1.5%) and heparin patients (1.8%). In the Hirulog group 1.8% (17 patients) of patients with normal platelet counts at study entry had low counts at

study completion; in the heparin group 2.0% (19 patients) of patients had a shift from normal to low platelet counts.

As for Study C92-304-1, though the protocol indicated that patients who had had prior exposure to Hirulog or who had participated in other blinded Hirulog studies would have plasma collected for determination of antibodies to Hirulog, no results for any determinations are given in the study report.

Reviewer's comments:
In this study the sponsor's protocol specified criteria for demonstrating efficacy of Hirulog were not met. In the overall population statistically significant superiority of Hirulog over heparin was not demonstrated for any of the primary or secondary efficacy endpoints. In fact, for one of the secondary endpoints, impending AVC, Hirulog appeared to be significantly worse than heparin ($p=0.009$). The only suggestions of superior efficacy of Hirulog were seen in the post-MI patient stratum which constituted about 15% of the study population. In this stratum a statistically significant benefit of Hirulog over heparin was seen in proportion of patients requiring revascularization (2% Hirulog, 8% heparin, $p=0.017$) and the combined endpoint of death, MI or revascularization (3% Hlrulog, 12% heparin; $p=0.001$). Marginal superiority of Hirulog was seen for death or MI, death, and overall procedural failure. In the non-post-MI patient stratum, for all the efficacy endpoints the performance of Hirulog was either no better or tended to be worse than that of heparin.

With regard to the conduct of the study, a sizeable number (about 7%) of patients (81 Hirulog, 91 heparin) who were randomized to double-blind treatment did not in fact receive study medication. Though the protocol called for information to be collected on any patients who were randomized but did not receive study medication, this was not done. Therefore, nothing is known about what was done for these patients and their outcomes. Also, about 16% of patients (188 Hirulog, 175 heparin) who received some study drug were discontinued prematurely due to unspecified "other" reasons.

Even though the study was prospectively stratified, it is notable that the post-MI patients represented only about 15% of the total patients randomized. Also, among these patients the most common protocol violation was misrandomization which involved 26/332 (7.8%) of the post-MI patients who were randomized and received study drug (26 patients [11 Hirulog, 15 heparin]). Of the 9 post-MI patients treated with Hirulog who had procedural failure, 1 had been misrandomized. Of the 22 post-MI patients treated with heparin who had procedural failure, 4 had been misrandomized. It should be kept in mind that for these studies the pharmacists who prepared the study drugs at the sites were not blinded to the treatments.

Follow-up Angiography Study:
Title: Protocol C93-319-P: Follow-up Assessment of Restenosis Following Percutaneous Transluminal Coronary Angioplasty (PTCA) in a Subset of Subjects Who Participated in Studies C92-304-1 and C92-304-2 with BG8967 and Heparin (NDA Vol. 1.149, pp. 3 through 68)

The sponsor has not submitted a full report for this study. Only a published abstract summarizing study results and the protocol for the study are included in the application. The information submitted is summarized here.

This was a randomized, double-blind, multicenter trial designed to evaluate the incidence of restenosis as measured by clinical or angiographic criteria in a subset of patients who had

participated in Studies C92-304-1 and C-92-304-2. In this study a subset of up to 500 patients who were treated with study medication (at least 15 hrs of infusion) and underwent successful PTCA in Studies C92-304-1 and C92-304-2 were to have follow-up angiography 3 to 6 months after completion of their participation in Study C92-304-1 or Study C92-304-2. Restenosis was to be analyzed using two angiographic endpoints: (1) an increase of the diameter stenosis from <50% after angioplasty to ≥50% at follow-up and (2) a continuous outcome based on the cumulative distribution of the follow-up percent diameter stenosis and absolute lumen diameter. Patients having worsening of clinical status could have follow-up angiograms done earlier than 3 months after study completion. The procedure for the selection of the subset of patients is unclear. The protocol indicates that: "Those sites participating in study C92-304-1 or C92-304-2 and in study C93-319-P will prospectively ask subjects currently participating under protocol C92-304-P to participate in protocol C93-319-P. Subjects will understand that actual participation requires a successful PTCA under protocol C92-304-P." The protocol for C93-319-P also called for an interim analysis to be done when 180 follow-up angiograms had been done. Adverse events occurring immediately prior to start of follow-up angiogram up to hospital discharge were to be recorded.

Investigators participating in this study were E. Deutsch, A. Dodek, R. Feldman, M. Frey, A. Gershlick, K. Ghalili, R. Ivanhoe, T. Kelly, P. Kraft, R. Magorien, J. Mann, M. Rothman, M. Schweiger, M. Shawl, M. Stillabower, J. Strony, and J. Vita. Ten were from Study C92-304-1 and 7 were from Study C92-304-2.

Results: Follow-up angiograms were obtained at a mean of 4.4±2.0 months after Study C92-304-1 or C92-304-2 PTCA. There was no statistically significant difference in restenosis rate between the Hirulog and heparin groups. The restenosis rate for Hirulog was 68% and for heparin was 61%. The late loss in lumen diameter was 0.34mm for Hirulog and 0.32mm for heparin. Restenosis rates (in both treatment groups) were increased in patients with diabetes and LAD location of lesion.

Reviewer's comments:
The summary results of this study suggest that, relative to heparin-treated patients, patients treated with Hirulog during PTCA do not have lower rates of restenosis at 3-6 months after PTCA. In fact there is a trend toward a higher rate of restenosis in the Hirulog-treated patients. The sponsor should submit the full report for this study. Also, the sponsor should analyze separately the restenosis rates for non-post-MI patients and post-MI patients.

OVERALL SAFETY ASSESSMENT:
During clinical development Hirulog has been used in a total of 3873 patients/subjects. This includes 2452 patients undergoing PTCA, 936 patients with unstable angina or acute myocardial infarction, 251 patients with venous thrombosis, 20 patients with heparin induced thrombocytopenia/heparin-induced thrombocytopenia with thrombosis syndrome (HIT/HITTS), and 195 normal subjects (some with renal failure).

Percutaneous Transluminal Coronary Angiography (PTCA): The safety results are summarized below for patients treated with Hirulog while undergoing PTCA.

Summary of Adverse Events in PTCA Controlled Trials (C92-304-1 and C92-304-2)

	All Patients		Non-Post MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Total number of patients	2161	2151	1792	1779	369	372
Total duration (hrs) of study drug administration (mean)	15.95	15.62	15.85	15.60	16.41	15.73
Total amount of study drug administered (mean)[1,2]	12.57	428.37	12.50	426.70	12.94	436.39
Number of patients who received:						
Bolus #1	2159 (>88)	2150 (>99)	1790 (>99)	1778 (>99)	369 (100)	372 (100)
Bolus #2[3,4]	1122 (46)	671 (31)	922 (51)	531 (30)	200 (54)	140 (38)
Bolus #3[3,4]	568 (23)	211 (10)	461 (26)	168 (9)	107 (29)	43 (12)
Number of patients with study drug dose reduction	50 (2)	204 (9)	42 (2)	182 (10)	8 (2)	22 (6)
Number of patients administered heparin prior to study drug	1321 (61)	1393 (66)	1007 (56)	1071 (60)	314 (86)	322 (87)
Number of patients administered concomitant heparin	53 (2)	27 (1)	17 (<1)	18 (1)	13 (4)	9 (2)
Number of patients administered heparin after discontinuation of study drug	436 (20)	432 (20)	348 (19)	339 (19)	88 (24)	93 (25)
Number of patients with treatment emergent adverse events	1776 (82)	1785 (83)	1468 (82)	1474 (83)	308 (83)	311 (84)
Number of patients with treatment emergent serious adverse events	34 (2)	40 (2)	32 (2)	27 (2)	2 (<1)	13 (3)
Number of patients with treatment emergent major bleeding events	79 (4)	199 (9)	70 (4)	155 (9)	9 (2)	44 (12)
retroperitoneal bleed	5 (<1)	15 (<1)	4 (<1)	14 (<1)	1 (<1)	1 (<1)
intracranial bleed	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Number of study discontinuations due to adverse events	24 (1.1)	32 (1.5)	17 (<1)	25 (1)	7 (2)	7 (2)
Number of deaths						
during hospitalization	9 (0.4)	6 (0.3)	9 (0.5)	3 (0.2)	0 (0)	3 (0.8)
at 6-month follow-up	28 (1.3)	20 (0.9)	22 (1.2)	15 (0.8)	6 (1.6)	5 (1.3)
total	37 (1.7)	26 (1.2)	31 (1.7)	18 (1.0)	6 (1.6)	8 (2.2)

[1] Amount includes all boluses and infusions
[2] Amount in mg/kg Hirulog, U/kg heparin
[3] Administered if ACT < 350 secs.
[4] Bolus #2 and Bolus #3 contained placebo for patients in the Hirulog treatment group and contained heparin (60U/kg) for patients in the heparin treatment group.

numbers in parentheses are percent of treated patients

reviewer's table, based on sponsor's tables, NDA Vols. 1.52, pp. 105, 110, 164 and Vol. 1.53, pp. 54 through 100, Vol. 1.54, pp. 34, 37 193 and Vol. 1.55, p 90, 206 through 221

Hirulog patients had somewhat more boluses of study drug and fewer dose reductions than did heparin patients, probably reflecting the generally lower ACT values in the Hirulog as compared to heparin patients in these two studies. About 20% of patients received heparin after completion of study participation. The incidence of treatment-emergent major bleeding events was lower in the Hirulog patients than in the heparin patients.

[Note: Treatment-emergent adverse events were defined as any event satisfying one of the following criteria:

- The event had a start date and time which was on or after the start date and time of initial study drug administration;
- The event had a start date on the same date as the initial start of study drug administration, and the event stop date is either missing or after the initial start of study drug administration, and the event start time was unavailable;
- The event had an unavailable start date and time and the event stop date and time is after the initial start of study drug administration date and time].

All Patients: The incidences of major bleeding events among all patients treated for any indication in any study are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Summary of Incidence of Treatment-Emergent Bleeding Events

	All PTCA Patients		PTCA Post-MI Patients		Unstable Angina and Acute MI Patients		Venous Thrombosis Patients		All Patients	
	Hirulog n=2452	Heparin n=2151	Hirulog n=369	Heparin n=372	Hirulog n=936	Heparin n=247	Hirulog n=251	Heparin	Hirulog n=3639	Heparin n=2398
Bleeding Events	1276 (52)	1699 (79)	196 (53)	266 (72)	337 (36)	122 (49)	69 (27)	---	1682 (46)	1821 (76)
Major bleeding Events	79 (4)	199 (9)	9 (2)	44 (12)	73 (8)	47 (19)	---	---	152 (5)	246 (10)
Serious Bleeding Events	35 (1)	89 (4)	5 (1)	13 (3)	14 (1)	10 (4)	0	---	49 (1)	99 (4)
Discontinuations Due to Bleeding	25 (1)	124 (6)	2 (<1)	16 (4)	21 (2)	23 (9)	3 (1)	---	49 (1)	147 (6)

sponsor's table modified, NDA Vol. 1.52, p. 192

The incidence of nonbleeding adverse events was similar among the various indications ranging from 62% to 83% of patients having some nonbleeding adverse event with Hirulog and 59% to 84% of heparin treated patients having some nonbleeding adverse event. The most frequent nonbleeding adverse events among all patients were back pain (30% of Hirulog, 41% of heparin), headache (13% of Hirulog, 10% of heparin), nausea (13% of Hirulog, 15% of heparin), pain (13% of Hirulog, 16% of heparin), hypotension (10% of Hirulog, 17% of heparin), fever (7% of Hirulog, 6% of heparin) and injection site pain (6% of Hirulog, 12% of heparin). Among the various indications, the types of adverse events were similar except that more venous thrombosis patients had constipation (15%).

The incidence of death among all patients is summarized by indication in the following table:

Overall Incidence of Patient Deaths

	PTCA Patients		Unstable Angina and Acute MI Patients		Venous Thrombosis Patients	
	Hirulog n=2452	Heparin n=2151	Hirulog n=936	Heparin 247	Hirulog n=251	Heparin
Total Deaths	43 (1.8)	26 (1.2)	36 (3.8)	12 (4.9)	0	—
Related Deaths	1 (<0.1)	1 (<0.1)	6 (0.6)	4 (1.6)	0	—
Cardiovascular Deaths	22 (0.9)	14 (0.7)	32 (3.4)	8 (3.2)	0	—

from sponsor's table, NDA Vol. 1.52, p. 223

Most deaths appeared to be related to underlying cardiovascular disease.

Among healthy subjects treated with Hirulog (109 subjects) about 66% reported some adverse event. Most frequent events were nausea (17%), headache, (16%), dizziness (15%), and injection site pain (11%).

The incidence of allergic reactions and rash in Hirulog-treated patients was low. One patients treated with Hirulog and no patients treated with heparin had an allergic-type adverse event that was attributed to study drug. In four studies (C90-010, C90-029, C90-039, and C90-041) 494 subjects were tested for antigenicity to Hirulog by enzyme-linked immunoassay. In one study 9/189 subjects tested initially showed a positive result but when repeat testing was done, values were negative. No subject having multiple exposure to Hirulog had a positive test for Hirulog antibody. Two subjects, patient #0902 (1.8mg/kg/hr group) in Study C90-041 and one patient in C93-313 had a positive post-Hirulog antibody test. Neither of these patients had clinical signs of allergic reaction. Patient #0902 was a 68 year old white man with obstructive pulmonary disease, coronary artery disease, history of myocardial infarction, seizure disorder and allergy to penicillin. On Hirulog treatment WBC were elevated (8.4 baseline, 14.1 on Hirulog); no differential was done. There were no adverse events reported for this patient, though hemoglobin declined from 14.0 to 13.1. He showed restenosis on follow-up tread-mill test 6 months after study.

REVIEWER'S DISCUSSION:

Efficacy: The pivotal clinical trials (C92-304-1 and C92-304-2) were designed to detect a 33% reduction in the incidence of procedural failure for the Hirulog group as compared to the heparin group. Both these studies failed in that regard. One study (C92-304-2) suggested superiority of Hirulog as compared to heparin for this endpoiont in 332 patients developing angina between 4 hrs and 2 weeks following myocardial infarction. However, this result was not seen in Study C92-304-1 which had a larger population of post-MI

patients (409 patients). Only for the combined endpoint of "death or MI" in post-MI patients was there a statistically significant benefit of Hirulog over placebo in both studies.

The sponsor has performed a post-hoc analysis to demonstrate equivalence of Hirulog and heparin with regard to the incidence of ischemic complications; however, the studies were not designed to demonstrate equivalence. The sponsor also performed an efficacy analysis on the combined data from Studies C92-304-1 and C92-304-2. In that analysis for the post-MI stratum 19/369 (5.1%) of Hirulog patients and 40/372 (10.8%) of heparin patients suffered procedural failure. This difference between treatment groups was statistically significant with a p-value of 0.004. However, even in the combined populations for the two studies, there was no statistically significant difference in primary efficacy endpoint, the procedural failure incidence for Hirulog as compared to heparin (123/2161 (5.7%) vs. 145/2151 (6.7%), p-value=0.148).

In summary, Studies C92-304-1 and C92-304-2 definitely do not demonstrate superiority of Hirulog over heparin for the primary endpoint and are equivocal for the secondary endpoints. The studies were not sized to demonstrate equivalence and the results are not robust enough to be certain of non-inferiority of Hirulog as compared to heparin. The strongest efficacy result was seen in the post-MI stratum which represented less than 20% of the total patients randomized. Even though the two studies were done using the same protocol the efficacy result seen in C92-304-2 for the post-MI stratum was not replicated in Study C92-304-1 which had a larger number of these post-MI patients. Therefore, the sponsor has not demonstrated efficacy of Hirulog by any of the protocol defined measures of effectiveness.

An additional relevant issue for this application is the fact that though it is standard practice to anticoagulate patients undergoing PTCA with heparin, adequate and well-controlled studies have not been done to demonstrate effectiveness of heparin for this indication and heparin is not labeled for this indication. Furthermore, evaluation of heparin for use in PTCA (and evaluation of the data in the current submission) is complicated further by the fact that though heparin is widely used in PTCA there does not appear to be a standard regimen or accepted schedule of treatment for the procedure. Note that for the current studies the heparin regimen to be used was changed in an amendment to the protocol for Studies C-92-304-1 and C-92-304-2 from "males: a bolus dose of 12,000 units with continuous infusion of 1,000 units/hr; females: a bolus dose of 10,000 units with continuous infusion of 800 units/hr" to bolus injection of 175 units/kg (with additional boluses of 60 units/kg, if needed) followed by infusion of 15 units/kg/hr. This major change in the heparin dosing is consistent with some uncertainty as to the proper use of heparin in PTCA. Interestingly, a fairly large proportion of patients (about 20%) received heparin after discontinuation of study drug. It is not clear whether this heparin was subcutaneously administered or intravenous or what doses, timing and duration were used. This might further blur assessment of the possible efficacy of Hirulog.

Safety: The sponsor claims greater safety of Hirulog as compared to heparin in these two studies. Examination of the safety database shows fewer and less severe bleeding events in the patients treated with Hirulog as compared to those treated with heparin. However, because heparin patients tended to have higher ACT values (longer clotting times), it is not clear that this may not at in part be due to the dose of heparin used. The distribution of 45 minute ACT values in Studies C92-304-1 and C92-304-2 is shown in the table below:

Distribution of 45-min ACT Values in Studies C92-304-1 and C92-304-2 (Intent-to-Treat Population)[a]

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Study C92-304-1:						
Number (%) of Patients Having ACT Values:						
<200	14 (1)	18 (2)	11 (1)	13 (2)	3 (1)	5 (1)
200 - 300	185 (17)	70 (7)	144 (17)	51 (6)	41 (20)	19 (9)
>300 - 350	329 (31)	179 (17)	273 (32)	142 (17)	56 (27)	37 (18)
>350	524 (48)	774 (73)	422 (49)	638 (74)	104 (50)	136 (67)
No ACT values	17 (2)	19 (2)	15 (2)	13 (2)	2 (1)	6 (3)
Total Patients	1071 (100)	1060 (100)	865 (100)	857 (100)	206 (100)	203 (100)
Study C92-304-2						
Number (%) of Patients Having ACT Values:						
<200	9 (1)	16 (1)	8 (1)	14 (2)	1 (1)	2 (1)
200 - 300	219 (20)	69 (6)	178 (19)	54 (6)	41 (25)	15 (9)
>300 - 350	329 (30)	212 (19)	275 (30)	174 (19)	54 (33)	38 (22)
>350	524 (48)	787 (72)	457 (49)	673 (73)	67 (41)	114 (67)
No ACT values	9 (1)	7 (1)	9 (1)	7 (8)	0 (0)	0 (0)
Total Patients	1090 (100)	1091 (100)	927 (100)	922 (100)	163 (100)	169 (100)

[a] numbers given are number of patients and (in parentheses) percent of patients

reviewer's original table, based on information in sponsor's tables, NDA Vol. 1.71, pp. 349 through 357 and Vol. 1.112 pp. 333 through 341

CONCLUSIONS AND RECOMMENDATIONS:

I recommend that Hirulog not be approved for use as anticoagulant in percutaneous transluminal coronary angioplasty (PTCA). The sponsor has failed to demonstrate efficacy of the drug by the protocol-specified criteria for which the study was designed. Major deficiencies with regard to efficacy include:

- No statistically significant benefit in either of the pivotal studies for the primary efficacy endpoint (procedural failure).
- Lack of consistency in results for secondary endpoints across the two identical pivotal studies.

The further investigation and development of this drug may benefit from Advisory Committee discussion of appropriate comparator anticoagulant regimens to use in future clinical trials for this indication.

/S/

Kathy M. Robie-Suh, M.D., Ph.D.

10/6/98

cc:
NDA 20-873
HFD-180
HFD-180/LTalarico /S/ 10-6-98
HFD-180/KRobie-Suh
HFD-181/JDuBeau
HFD-180/JChoudary
HFD-180/EDuffy
HFD-720/MRashid
f/t 10/6/98 jgw

APPENDIX A

TIMI GRADE FLOW

Grade 0: No perfusion. No antegrade flow beyond the point of occlusion.

Grade 1: Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2: Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel (e.g. opposite coronary artery or the coronary bed proximal to the obstruction).

Grade 3: Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Grade 0 or
Grade 1: Signifies a closed artery.

Grade 2 or
Grade 3: Signifies an open artery with complete perfusion within at least three cardiac cycles.

from NDA Vol. 1.72, p. 296

CRITERIA FOR ASSESSMENT OF BLEEDING

Each subject in the study will be assessed for signs or symptoms of bleeding. Bleeding will be classified as follows:

MAJOR:
- if it is clinically overt with a fall in hemoglobin level of 3 g/dL (30 g/L) or more, or
- if it is clinically overt and leads to a transfusion of two or more units of blood, or
- if it is retroperitoneal, or
- if it is intracranial.

MINOR:
- if it is clinically overt but does not meet the other criteria for MAJOR bleeding.

from NDA Vol. 1.72, p. 297

APPEARS THIS WAY
ON ORIGINAL

DEFINITIONS

Myocardial infarction

A 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 2 x upper limits of normal and CK-MB 4%; (3) new development of 2 step Minnesota Q[16] wave codes or new left bundle branch block (not rate related).

Abrupt vessel closure

Total or subtotal occlusion of the vessel after attempted angioplasty with corresponding TIMI Grade 0-1 flow (Appendix I) with or without associated symptoms or signs of ischemia within 24 hours of PTCA.

Lesion complexity

Graded as A, B1, B2, or C according to the Abrupt Vessel Closure-AHA Task Force definitions as modified by Ellis et al[17]

Type A <10 mm, discrete, concentric, readily accessible, <45 angle, smooth contour, little or no calcification, less than totally occluded, not ostial, no major sidebranch involvement, absence of thrombus

Type B1 one of the following characteristics:

Type B2 two or more of the following characteristics:

10-20 mm, tubular, eccentric, moderate tortuosity of proximal segment, irregular contour, moderate to heavy calcification, total occlusion <3 mos, ostial or bifurcation lesion requiring two guidewires

Type C >20 mm, diffuse, excessive tortuosity of proximal segment, total occlusion >3 mos, inability to protect major sidebranches, degenerated vein graft [2,3]

Diffuse disease

Presence of >20 mm segment of contiguous stenosis >50% severity

Dissection type

Classified as

A radiolucent areas, often linear, within the coronary lumen during contrast injection with minimal or no persistence of contrast after the dye has cleared;

B parallel tracts of double lumen separated by a radiolucent area during contrast injection with minimal or no persistence after dye clearance;

C contrast outside the coronary lumen with persistence of contrast in the area after clearance of dye from the coronary lumen;

D spiral luminal filling defects, frequently with extensive contrast staining of the vessel[4]

Eccentricity

A stenosis asymmetrically positioned in any angiographic view

Coronary flow

Classified per TIMI flow grades

Spasm

A tapered decrease in vessel diameter, reversible with sublingual, intravenous or intracoronary nitroglycerin

Stenosis in a bend

>45 angulation

Thrombus

Presence of a filling defect, which may be globoid, usually located immediately downstream from a stenosis; an area of contrast staining noted within the stenosis to be dilated[6]; or evidence of embolization

Tubular lesion

Lesion length of 10-20 mm

from NDA Vol. 1.72, p. 298