Summary of Interim Analysis Results of Ongoing Studies in PTCA

Study	Indication	Design	No. of Patients	Treatments	Results
Study TMC-97-01 (CACHET Pilot Study B) (U.S.; 4/99-ongoing) (NDA Vol. 20.8)	elective PTCA or intracoronary stent	open-label, randomized, 2:1 ratio, Hirulog:heparin/ReoPro	planned for 100 pts; 62 enrolled so far (43, Hirulog/ReoPro; 19 heparin/ReoPro)	bivalirudin 0.5mg/kg IV bolus followed by a 1.75mg/kg/hr iv infusion (+ ReoPro 0.25mg/kg bolus followed by 0.125ug/kg/min infusion (up to 10 ug/min) for 12 hrs as needed. vs. ReoPro iv bolus of 0.25mg/kg followed by infusion of 0.125ug/kg/min (up to 10ug/min) for 12 hrs plus low-dose weight adjusted heparin for the duration of the procedure (target ACT 200 sec) All pts received 325mg aspirin.	1 Hirulog/ReoPro patient and 4 heparin/ReoPro patients received less than full dose of study drug; 1 Hirulog/ReoPro patients and 0 heparin/ReoPro patients discontinued study drug because of adverse event; maximum median ACT was greater in Hirulog/ReoPro patients than in heparin/ReoPro pts (311 vs 294); 3 Hirulog/ReoPro pts vs 0 heparin/ReoPro pts suffered MI after PTCA; 2 repeat PTCA and 1 stent placement in heparin/ReoPro group vs 0 in Hirulog/ReoPro group; 2 major bleeds in Hirulog/ReoPro, 1 in heparin ReoPro; 2 transfusions (PRBC) in Hirulog/ReoPro, none in heparin/ReoPro.no strokes, deaths or urgent revascularizations. No difference between treatment groups in any serious clinical outcomes.
TMC-99-05 (Swedon; 5/99-ongoing)) (NDA Vol. 20.9)	PCI (PCTA or stent) in pts who received LMWH for ≥24hrs for management of acute coronary syndromes (ACS)	open-label, randomized	planned for 40 pts; 40 pts enrolled (20 Hirulog, 20 heparin)	bivalirudin 1.0mg/kg iv bolus followed by infusion at 2.5mg/kg/hr for up to 4 hrs vs. heparin to a target ACT of >300secs (225 sec if ReoPro use is planned). It was recommended that heparin use be discontinued if the pt was stable at the end of the procedure	(note: enrollment is completed but followup is continuing). Most pts treated with balloon and stent. Safety followup to be 30 days; interim report includes followup to 7 days. All pts received study medication as per protocol. Median ACT in Hirulog group at 30 min post-bolus = 354 sec; in heparin group = 258 sec. One pt in heparin group suffered MI. No deaths, major hemorrhage or AE withdrawals. ReoPro given in 2 Hirulog and 8 heparin patients during and/or after procedure.
TMC-98-20 (Australia-New Zealand); 4/99-ongoing) (NDA Vol. 20.10)	PCI with stenting	open-label, randomized	planned for 30 pts; 13 enrolled so far (6 heparin + ticlopidine; 7 bivalirudin + ticlopidine)	ticlopidine 250mg BID for 48-72 hrs prior to study entry was given in all pts. Then pts were randomized to: bivalirudin 1mg/kg bolus followed by a 2.5mg/kg/hr infusion for 4 hrs or heparin 10,000IU bolus with the intention of obtaining a target ACT >300sec. All pts received aspirin (300mg daily).	ACT values in the bivalirudin + ticlopidine group were higher than in the heparin + ticlopidine group (355 vs. 261 at 10 min); P-selectin values suppressed in both groups (no interference of bivalirudin or heparin on antiplatelet effects of ticlopidine and aspirin). No deaths. One MI in the heparin + ticlopidine group, associated with subacute stent thrombosis. No urgent revascularizations./ No serious adverse events. No "major bleeding episode related to the study treatments during the study period". [Reviewer note: Total major bleeding not reported].
TMC-98-09 (Australia-New Zealand); 4/99-ongoing) (NDA Vol. 20.11)	PTCA in pts with normal, mild or moderately impaired renal function	open-label, PK/PD study	planned for 30 patients; 11 enrolled so far (	bivalirudin 1mg/kg iv bolus followed by a 2.5mg/kg/hr infusion x 4 hrs, followed by a 0.5mg/kg/hr infusion x 4 hrs. All pts received aspirin (300mg daily)..	Sponsor found similar PK results in normal and mild renal impairment for all parameters except Tmax which was slightly longer. In moderal renal failure, AUC and Cmax were markedly higher and total clearance was decreased; however, ACT time curves were similar regardless of renal status.. Renal clearance was about 20% of total clearance. No major blooding episodes or deaths. No serious adverse events judged to be associated with bivalirudin and occurring within 7 days of bivalirudin administration. [Reviewer note: Total serious AEs not reported].

Other studies which are ongoing are:
(1) the PK/PD Renal Impairment study where 11 patients have been enrolled. Nine patients have received stents. There have been no serious adverse events, major hemorrhage or unexpected laboratory findings.
(2) HERO-2, where 400 acute MI patients have been enrolled. No study data is yet available to the sponsor. There has been one IND safety report – "drug hypersensitivity reaction" in a patient who received bivalirudin + [redacted]
(3) HIT/HITTS study, where 4 patients have been enrolled. There have been no deaths, urgent revascularizations, myocardial infarctions, major hemorrhages or withdrawals in the study.

Regarding foreign marketing the sponsor states: "In July 1999, The New Zealand Ministry of Health approved the New Drug Application for the marketing of bivalirudin in New Zealand. At this time; a final product label has not been negotiated or approved and the product is not yet being marketed in New Zealand." Applications for to market bivalirudin also have been filed in Canada and the European Union.

Discussion:
In the following table I have summarized the more important of the new and old efficacy analyses for this application. Results are presented and statistically compared using odds ratios (since this is the predominant way in which the sponsor's analyses have been submitted). Data from the two trials (Study C92-304-1 and Study C92-304-2) are pooled for analysis as well as having analyses done for each study separately.

Summary of Efficacy Comparisons: Odds Ratios for Bivalirudin as Compared to Heparin[●]

	To end of Hospitalization (original)[a]			Through 7 days or end of hospitalization[b]			Through 30 days of Followup[b]			Through 180 Days of Followup[b]		
	All Patients	Non-Post-MI Patients	Post-MI Patients	All Patients	Non-Post-MI Patients	Post-MI Patients	All Patients	Non-Post-MI Patients	Post-MI Patients	All Patients	Non-Post-MI Patients	Post-MI Patients
Study C92-304-1 and Study C92-304-2 Combined:												
Procedural failure[c]	0.89 NS	1.03 NS	0.45 (0.25,0.79)	0.84 NS	0.92 NS	0.55 (0.33,0.93)	0.89 NS	0.99 NS	0.55 (0.34,0.86)	0.91 NS	0.96 NS	0.71 NS
Death, MI, or Revasculariz ation	0.83 NS	0.99 NS	0.34 (0.17,0.66)	0.78 (0.62,0.99)	0.87 NS	0.47 (0.26,0.84)	0.86 NS	0.98 NS	0.48 (0.29,0.80)	0.90 NS	0.95 NS	0.86 NS
Major hemorrhage	0.35 (0.27,0.46)	0.41 (0.30,0.54)	0.16 (0.08,0.34)	0.34 (0.26,0.45)	0.39 (0.29,0.52)	0.16 (0.08,0.34)	0.35 (0.27,0.46)	0.41 (0.30,0.54)	0.16 (0.08,0.34)	0.35 (0.27,0.46)	0.41 (0.30,0.54)	0.16 (0.08,0.34)
Study C92-304-1:												
Procedural failure[c]	0.83 NS	0.92 NS	0.52 NS	0.80 NS	0.82 NS	0.71 NS	0.84 NS	0.90 NS	0.62 NS	0.91 NS	0.95 NS	0.78 NS
Death, MI, or Revasculariz ation	0.81 NS	0.88 NS	0.53 NS	0.80 NS	0.80 NS	0.79 NS	0.86 NS	0.92 NS	0.66 NS	0.92 NS	0.95 NS	0.86 NS
Major hemorrhage	0.36 (0.25,0.51)	0.38 (0.26,0.57)	0.25 (0.11,0.58)	0.34 (0.24,0.49)	0.36 (0.24,0.54)	0.25 (0.11,0.58)	0.36 (0.25,0.51)	0.38 (0.26,0.57)	0.25 (0.11,0.58)	0.36 (0.25,0.51)	0.38 (0.26,0.57)	0.25 (0.11,0.58)
Study C92-304-2												
Procedural failure[c]	0.96 NS	1.15 NS	0.39 (0.17,0.88)	0.89 NS	1.03 NS	0.43 (0.20,0.92)	0.94 NS	1.09 NS	0.48 (0.25,0.93)	0.91 NS	0.97 NS	0.65 NS
Death, MI, or Revasculariz ation	0.86 NS	1.13 NS	0.22 (0.08,0.60)	0.77 NS	0.95 NS	0.28 (0.12,0.68)	0.86 NS	1.05 NS	0.37 (0.18,0.75)	0.89 NS	0.96 NS	0.58 (0.35,0.97)
Major hemorrhage	0.35 (0.23,0.53)	0.44 (0.28,0.68)	0.04 (0.01,0.32)	0.34 (0.22,0.52)	0.42 (0.27,0.66)	0.04 (0.01,0.32)	0.35 (0.23,0.53)	0.44 (0.28,0.68)	0.04 (0.01,0.32)	0.35 (0.23,0.53)	0.44 (0.28,0.68)	0.04 (0.01,0.32)

● Numbers less than 1.00 indicate bivalirudin better than heparin.

[a] Using original data and definitions; [b] using revised MI definition; [c] Original primary endpoint; composite consisting of death, MI, revascularization, and abrupt vessel closure

reviewer's table, information from sponsor's tables, NDA Vol. 15.2, pp. 283, 284, 285, and 344 through 352.

The additional analyses the sponsor has done do not contribute significant new information to support efficacy of bivalirudin in PTCA. The results are consistent with what already has been shown for Studies C92-304-1/2, namely, that there is less bleeding with bivalirudin in both non-post-MI patients and post-MI patients. Even when the two studies are combined, superiority of bivalirudin over heparin for procedural failure is demonstrated only for the post-MI patient group and that result is driven mainly by Study C92-304-2.

Conclusions and Recommendations:
There is ample evidence from pre-clinical and clinical studies that bivalirudin is an anticoagulant. The information provided in this application supports that bivalirudin, like heparin, is an antithrombotic agent. However, the sponsor has not adequately demonstrated clinical effectiveness of bivalirudin in PTCA. Specifically:

- No statistically significant benefit for the primary efficacy endpoint (procedural failure) was achieved in either of the pivotal studies. The efficacy benefit seen in the secondary efficacy endpoints reflected predominantly the effect of the bivalirudin in the post-MI population. (Also, it should be noted that at 6 month followup in both studies there were numerically more deaths in the bivalirudin groups (17 and 20) as compared to the heparin group (11 and 15).
- The efficacy analyses suggesting a benefit of bivalirudin over heparin are confounded by the fact that there was non-random use of heparin in the periprocedure period in a majority of the patients in both treatment arms.
- The dosing used in the clinical trial (bolus of bivalirudin followed by infusion for up to 24 hrs (mean infusion time 18 hrs)) does not provide sufficient information to adequately label the drug for safe and effective use in PTCA as currently conducted in the United States. The American College of Chest Physicians currently recommends use of heparin bolus(es) during PTCA (to target ACT), early sheath removal when the ACT falls to less than 150 to 180 sec following the procedure, and does not recommend routine post-procedural infusion of heparin.
- The bleeding benefit observed in both studies could have been due to the relatively aggressive heparin regimen used as comparator and the lack of usual aPTT monitoring.

The sponsor has provided evidence from the literature to support the customary use of heparin in some regimen for thromboprophylaxis during PTCA, although the evidence for effectiveness of heparin is not sufficient to support labeling of heparin (including dosing recommendations) for that indication. This view appears to be supported by the recent recommendations of the American Academy of Chest Physicians which recommend use of heparin during but not routinely after PTCA and acknowledge that the recommendation is based nonrandomized concurrent cohort studies.

The results of Studies C92-304-1 and C92-304-2, combined, are consistent with bivalirudin (as given in these studies) not being significantly worse than heparin (as given and monitored in these studies) for prevention of procedural failure in PTCA. Bivalirudin could have been up to 1-2% (absolute values) worse than heparin in these studies with regard to the primary endpoint (10%-25% (relative values)) (personal communication, MRashid, FDA Statistical Reviewer). However, these trials were not designed as non-inferiority trials.

The sponsor should consider further investigation of the use of bivalirudin for PTCA in post-MI patients.

/S/
Kathy M. Robie-Suh, M.D., Ph.D. 10/6/99

cc:
NDA 20-873
HFD-180/Division File
HFD-180/LTalarico /S/ 10-6-99
HFD-180/SAurecchia
HFD-180/JChoudary
HFD-427/EDuffy
HFD-180/KRobieSuh
HFD-181/JDuBeau
HFD-180/PFlyer
HFD-180/MRashid
f/t 9/30/99 jgw
N/20873909.0KR

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

OCT - 6 1998

NDA:	NDA 20-873
Sponsor:	The Medicines Company One Cambridge Center Cambridge, Massachusetts 02142
Drug name:	Hirulog (bivalirudin) Injection
Date submitted:	December 23, 1997
Date received:	December 23, 1997
Date assigned:	January 5, 1998
Review completed:	October 5, 1998
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
Hirulog (bivalirudin) is a homogeneous synthetic 20-amino acid peptide which is a direct thrombin inhibitor and which is active against both clot-bound and circulating thrombin. In this application the sponsor seeks approval of bivalirudin as an alternative to heparin for use as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Though heparin is not approved for use in PTCA, it is commonly used for anticoagulation during the procedure.

PTCA is done to achieve revascularization in patients who have coronary artery disease. Procedural failure following PTCA most often is associated with abrupt closure of the dilated vessel due to a combination of vessel dissection, coronary spasm and/or thrombus formation. This procedural failure is associated with significant morbidity and mortality including myocardial infarction, death, or requirement for emergency coronary artery bypass graft surgery. The incidence rate of procedural failure following PTCA has been reported as 5 to 10% (Holmes, DR et al. J. Am Coll. Cardiol. 12:1149 (1988)).

Construction of a database for outcome of PTCA during current practice of medicine was done by Dr. John Bittl (Brigham and Women's Hospital, Boston, Massachusetts) and TIMI investigators using a multicenter (9 sites), prospective registry of clinical outcome in patients undergoing PTCA under Biogen sponsorship. Outcome data from that database are summarized in the following table:

Procedural Failure in Angioplasty Registry

Complication Type	Registry Data (n=591)	Data from the Literature with Heparin	Results from BG8967 in Study C90-041-P (1.8 +2.2 mg/kg/hr)
Any abrupt or impending closure	65/591 (11.0%)	4.4-8.3%	3.9%
Major ischemic complication (death, myocardial infarction, or emergency coronary artery bypass grafting)	45/591 (7.6%)	6%	2%
Closure or ischemic complication	97/591 (16.4%)	less than 10%	3.9%

The information in this database indicates that patients who undergo PTCA to restore patency of coronary arteries have a procedure failure rate ranging from 4.5% (National Heart, Lung, and Blood Institute (NHLBI), 1979-81) to 7.6% (Dr. J Bittl, Brigham and Women's Hospital, Boston, Massachusetts).

Lesions known to have poor outcome when dilated by balloon angioplasty and improved outcome when treated by eximer laser angioplasty include occlusive lesions in saphenous vein grafts that are over three years old, aorto-ostial lesions, and diffuse lesions greater than 20 mm in length.

Rationale for Use of Bivalirudin in Preventing Clot Formation:
Limitations of Heparin: Although use of heparin during PTCA is standard practice, heparin use is limited by several considerations including: inability of heparin to inactivate platelet-bound Factor X and clot-bound thrombin, unpredictable extent of desired pharmacologic effect, and an associated immune-mediated side effect known as heparin-induced thrombocytopenia (HIT) [also known as "heparin-associated thrombocytopenia (HAT)"], which occurs several days after initiation of heparin therapy.

Heparin inhibits clot formation indirectly, mainly by binding to antithrombin III (antithrombin) in the plasma thereby increasing antithrombin's activity against thrombin by 1000-fold. Heparin serves as a catalytic template to which both the thrombin and antithrombin, a serine protease, bind. Thrombin then cleaves a specific Arg-Ser peptide bond in antithrombin and in doing so becomes stably complexed with the antithrombin molecule. Antithrombin also inhibits activated clotting factors Xa, IXa, XIa, XIIa, and kallikrien and heparin strongly catalyzes the binding and inactivation of factor Xa by antithrombin as well as the binding and inactivation of thrombin by antithrombin . However, heparin is not able to bind to platelet-bound Factor Xa or to thrombin bound to fibrin, so these complexes remain in the circulation stimulating platelet aggregation and thrombus formation.

Heparin is a mucopolysaccharide composed of interlinked alternating chains of D-glucosamine and D-glucuronic acid. The polysaccharide chains vary in length and composition. Because heparin is a heterogeneous mixture of molecules having a variety of pharmacologic and pharmacokinetic properties, the anticoagulant effect of a given dose of heparin is unpredictable. Only about a third of heparin molecules have the site which allows binding to antithrombin and the consequent enhancement of the antithrombin anticoagulant activity. Also, heparin molecules that contain both the binding sites for thrombin and antithrombin are of higher molecular weight than the inactive heparin molecules and are cleared from the circulation more rapidly than the smaller inactive molecules. Finally, heparin binds

extensively to plasma proteins and endothelial cells further reducing the circulating pool of heparin available for the desired anticoagulation action. Consequently, heparin use most often require frequent monitoring of coagulation parameters (usually aPTT).

Heparin-induced thrombocytopenia (HIT) occurs when an IgG-heparin complex binds to platelets causing platelet activation and aggregation. This aggregation process can snowball depleting platelets in the plasma and causing widespread deposition of pale thrombi, a syndrome referred to as heparin-induced thrombocytopenia-thrombosis syndrome (HITTS). HIT/HITTS is a serious and sometimes fatal complication of heparin use.

Potential Advantages of Hirulog over Heparin: Bivalirudin is a potent and highly specific inhibitor of human alpha-thrombin *in vitro*. It binds directly to clot-bound thrombin as well as soluble thrombin causing inhibition of clot extension as well as of initial clot formation. The onset of action (like that of heparin) is rapid with intravenous administration and the effects rapidly resolve when infusion is discontinued. Anticoagulant activity, as measured by activated clotting time (ACT), is predictably correlated with drug dose and with plasma levels of the drug so there should not be a need for frequent monitoring of clotting times during drug administration. Finally, the sponsor reports that Hirulog does not cause platelet aggregation in sera from patients with HIT/HITTS.

Materials Reviewed:
This submission consists of 618 volumes. Contents of these volumes are as follows:

Volume 1.1	-	cover letter; diskettes with WP copies of ISE, ISS and reports of the Studies C92-304-1 and C92-304-2; overall table of contents; patent info.; user fee info.; and draft labeling
Volume 1.2	-	application summary
Volumes 1.3 through 1.7	-	Chemistry, Manufacturing, and Controls Information
Volumes 1.8 through 1.37	-	Nonclinical Pharmacology and Toxicology
Volumes 1.38 through 1.48 and 1.65 through 1.70	-	Human Pharmacokinetics and Bioavailability
Volumes 1.49 through 1.64 and 1.71 through 1.189	-	Clinical Data Section: controlled clinical studies; uncontrolled clinical studies; other studies and info.
Volume 1.190 through 1.192	-	Literature References
Volumes 1.193 (and controlled clinical study volumes)	-	Statistical Data Section
Volumes 1.194 through 1.525	-	Case Report Tabulations
Volumes 1.526 through 1.619	-	Case Report Forms (deaths and adverse events discontinuations)

For this review I have examined material in volumes 1.1, 1.2, 1.8, 1.38, the Clinical Data Section, Literature References, Case Report Tabulations and Case Report Forms.

Chemistry:
Chemical Structure: The chemical structure of bivalirudin is as follows:
D-Phe-Pro-Arg-Pro-Gly-Gly-Gly-Gly-Asg-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu

The bulk new drug substance is actually a di-trifluroacetate salt, hydrate. The molecular weight of the anhydrous free base peptide is 2180.3 and it molecular formula is $C_{98}H_{138}N_{24}O_{33}$. The drug product, Hirulog (bivalirudin) Injection, contains 250 mg of drug substance in a lyophilized, mannitol-based formula.

Manufacture: The drug product was studied under IND [redacted] by [redacted]. Rights were transferred to The Medicines Company in March 1997.

During development there have been 3 methods of synthesis of Hirulog. All three methods used the same protected amino acids and/or protected dipeptides as starting material. The Hirulog used in the initial clinical studies was synthesized using a solid phase chemistry manufacturing process. For the product used in the clinical efficacy trials, the manufacturing process was changed to a homogeneous liquid phase chemistry process. For commercial production the liquid phase chemistry process has been scaled up. [redacted]

For marketing the drug substance will be manufactured by [redacted] This company also will be responsible for quality control and perform stability studies for the bulk drug substance. The drug substance will be manufactured by [redacted], who will be responsible for quality control and stability studies for the drug product. [redacted] was the original and only manufacturer of the drug substance; [redacted] is one of the original contract manufacturers of the drug product for the investigational studies, and will be the only manufacturer of the commercial product.

Preclinical Pharmacology and Toxicology Information:
The application includes *in vitro* studies and *in vivo* studies in animals investigating the anticoagulant activity of Hirulog. Also, single dose and repeated dose toxicity studies and several drug interaction studies have been submitted. Other preclinical pharmacology studies submitted include reproductive and teratology studies, mutagenicity studies, ADME studies, and pharmacokinetic/pharmacodynamic studies in animals. The preclinical pharmacology studies are presented and discussed in some detail in the FDA Pharmacology review. Below I have summarized some of the major findings reported by the sponsor.

Absorption, Distribution, Metabolism, and Excretion (ADME): Hirulog is most likely proteolytically metabolized to individual L-amino acids which are then reincorporated into newly synthesized proteins in the body. Proteolysis also yields a D-Phe amino acid moiety which derives from the N-terminal portion of the polypeptide.

Hirulog is metabolized and excreted primarily by the kidney. Partial nephrectomy of rats resulted in decreased plasma clearance of the drug and prolonged the pharmacodynamic effects. In dogs infusion of Hirulog did not affect the glomerular filtration rate (GFR).

Pharmacologic Activity: Hirulog binds to free and clot-bound thrombin with a K_i of 2.3nM and inhibits thrombin activity with an IC_{50} of 0.014uM. Hirulog binds to thrombin at the same sites as hirudin, namely the active site and the anion binding site, but with 1/1000th the affinity of hirudin. The binding of Hirulog to the active site is reversible, with dissociation being accomplished by slow cleavage of the bivalirudin Arg_3-Pro_4. This reversibility allows recovery of the Protein C activation function of thrombin, which helps attenuate the coagulation cascade. However, Hirulog binding at the anion site is irreversible which continues to prevent thrombin mediated cleavage of fibrinogen and its platelet thrombin receptor.

Concentrations of Hirulog required to prolong coagulation times to 3x control values are estimated at 820ng/ml for activated partial thromboplastin time (aPTT), 2600ng/ml for prothrombin time (PT) and 86ng/ml for thrombin time (TT). Anticoagulant activity of Hirulog has been demonstrated *in vivo* and/or *in vitro* in all species tested, including human, cynomolgus monkey, rat, and mouse. Thrombin-induced platelet activation, and ensuing granule release, p-selectin expression, and aggregation are inhibited in a dose-dependent fashion.

Hirulog activity was not affected by platelet activation products and Hirulog does not appear to cause adverse platelet reactions *in vivo*.

Preclinical Toxicology: Studies in mice showed no evidence of neuropharmacologic or anticonvulsant activity. In the rat and dog there was a dose-related (1 and 5mg/kg) transient increase in diastolic and systolic blood pressure immediately post-dose but no increase in heart rate. However, no blood pressure increase was seen in monkeys and baboons.

Drug interaction studies in animals showed no increased adverse effects related to concurrent use of Hirulog with aspirin [redacted] Combination treatment of Rhesus monkeys with Hirulog, aspirin, tPA and heparin was associated with decreased activity of the animals, slight bleeding from rectum and/or pale color. Body weight decreased by 8% in the tPA/Hirulog group and there was more rapid increase in aPTT and TT with Hirulog/tPA than with heparin/tPA. There was greater increase in PT with Hirulog/TPA than with heparin/tPA. Clearance of tPA was decreased with Hirulog/tPA and heparin/tPA. In cynomolgus monkeys concurrent administration of Hirulog and urokinase gave a 5-6-fold increase in aPTT as compared to Hirulog alone. Concurrent administration of Hirulog and warfarin gave increased PT and aPTT.

Single-dose intravenous and subcutaneous studies up to 200mg/kg in rats and mice showed no adverse effects other than enlarged thymus in one mouse and in rats. Some rats developed respiratory distress and died a week after drug administration. Subsequent study with a different Hirulog solution showed no adverse effects.

Repeated dose toxicity studies were done in rats, rabbits and monkeys. A NOAEL of 25-80mg/kg/day was found in Sprague Dawley rats. Histopathological evidence of toxicity seen included hemorrhage in and around thymus, epididymis and epicardium. In the Cynomolgus monkey the NOAEL was 40-45mg/kg/day.

No pyrogenicity or evidence for anaphylaxis was seen in rabbits or guinea pigs. In rats and rabbits some effects on fertility and development (such as increased fetal resorptions, and decrease in live fetuses were seen at high doses of Hirulog general with a developmental NOEL of about 150mg/kg/day. Mutagenicity studies, including mouse micronucleus test, Ames testing, CHO cell testing, and human peripheral lymphocyte testing did not show any evidence of mutagenicity, clastogenicity or alterations in DNA.

Clinical Studies Summary:
The NDA application lists a total of 25 clinical studies that have been done using Hirulog. Ten of these were clinical pharmacology studies measuring pharmacokinetic and/or pharmacodynamic parameters and 15 were clinical efficacy and/or safety studies. The clinical pharmacology studies are discussed in the **Human Pharmacology** section of this review.

Two studies were pivotal efficacy trials in 4312 patients undergoing PTCA (Studies C92-304-1 and C92-304-2). Also, there were 8 trials involving 1183 unstable angina and acute myocardial infarction patients, 2 trials involving 251 venous thrombosis patients, and 2 trials involving 39 patients with heparin-induced thrombocytopenia/heparin-induced thrombosis. Finally, there was a follow-up angiographic study (Study C93-319) in a subset (253 patients) of the patients enrolled in Studies C92-304-1 and C92-304-2). Major features and results of these clinical efficacy and safety trials are summarized in the following table:

Table of Clinical Efficacy and Safety Studies

Study	Indication	Design	No. of Patients M/F (%); Age range	Treatments	Results
Controlled Studies in PTCA:					
C92-304-1 (multinational, predominantly U.S.)	unstable angina undergoing PTCA	MC, R, DB, PG, comparison of Hirulog and heparin stratified into post-infarction angina and non-post infarction angina	2318 randomized 2131 treated 67/33; 26-88yrs	Hirulog 1mg/kg IV bolus followed by 2.5mg/kg/hr IV infusion x 4 hrs followed by 0.2mg/kg/hr x up to 20hrs	primary efficacy endpoint: procedural failure: overall population Hirulog, 7.2%; heparin, 8.5%; post-MI pts (15% of total pop.), Hirulog, 4.9%; heparin, 8.9%, p=0.104; no clinically or statistically significant differences between treatments at 6-month follow-up. safety endpoint: major bleeding: overall population, Hirulog, 4.4%; heparin, 10.7%; post-MI population: Hirulog, 3.9%; heparin, 12.3%.
C92-304-2 (multinational, predominantly U.S.)	unstable angina undergoing PTCA	MC, R, DB, PG, comparison of Hirulog and heparin stratified into post-infarction angina and non-post infarction angina	2354 randomized 2181 treated 68/32; 27-90 yrs	Hirulog 1mg/kg IV bolus followed by 2.5mg/kg/hr IV infusion x 4 hrs followed by 0.2mg/kg/hr x up to 20hrs	primary efficacy endpoint: procedural failure: overall population Hirulog, 7.6%; heparin, 8.0%; post-MI pts (19% of total pop.), Hirulog, 5.5%; heparin, 13.0%, p=0.018; no clinically or statistically significant differences between treatments at 6-month follow-up safety endpoint: major bleeding: overall population: Hirulog, 2.9%; heparin, 7.9%; post-MI population: 0.6%, heparin, 11.2%.
C93-319 (multinational, predominantly U.S.)	unstable angina undergoing PTCA	MC, R, DB, PG, comparison of Hirulog and heparin	patients treated with Hirulog or heparin in Study C92-304-1 or C92-304-2; 253 patients enrolled, 137 patients evaluable	voluntary follow-up angiography of these patients 6 months after completing PTCA in Study C92-304-1 or C92-304-2.	Restenosis rates: Hirulog, 68%; heparin, 61%. (no stat. sig. difference)
Uncontrolled Studies in PTCA:					
C90-041	patients undergoing PTCA	MC, open-label, dose-ranging	303 82/18; 29-78 yrs		
Controlled Studies in Other Indications:					
C92-307 (HERO-1 Study) (multinational, including U.S.)	suspected acute MI	MC, R, DB, PG comparison of Hirulog + [redacted] vs. IV heparin + [redacted]	136 136 140 total 412 75/25; 28-87 yrs	(1) Hirulog 0.125 mg/kg IV bolus + 0.25mg/kg/hr IV infusion x 12 hr + 0.125 mg/kg/hr IV infusion x 36-48 hr (2) Hirulog 0.25mg/kg IV bolus + 0.5 mg/kg/hr x 12 hr + 0.25mg/kg/hr IV infusion X36-48 hrs (3) Heparin 5000 U IV bolus + 1000 U/hr IV infusion x 48-60 hrs (pts <80kg) or 1200 U/h IV infusion x 48-60 hrs (pts ≥80kg)	early patency: (1) 48%, (2) 46%, (3) 35% at 30-day follow-up no difference in sustained angiographic patency, angiographic reocclusion, number of ischemic episodes, and death or MI. Major bleeding: (1) 14.4%, (2) 19.5%), (3) 27.5% (stat sig. For (1) vs. (3)); hematuria more freq. in Hirulog: (1) 18%; (2) 22%; (3) 15% 24 Deaths: (1) 7; (2) 7; (3) 9; (1 pt died not treated)

C90-052 (U.S.)	elective diagnostic cardiac catheterization	single center, R, SB, PG, active control	16 15 16 total 47 71/29; 37-73 yrs	(1) heparin 5000 U IV bolus (2) Hirulog 0.05 mg/kg IV bolus + 0.2 mg/kg/hr IV infusion x 15-40 min (3) Hirulog 0.15mg/kg IV bolus + 0.6mg/kg/hr IV infusion x 13-35min	Coagulation parameters measured: aPTT, PT, TT, ACT, fibrinopeptide A. Anticoagulation achieved rapidly (within 5 min of dosing) and was predictable and dose-related. Most common adverse event: back pain. No major bleeding events.
C92-301 (TIMI-7) (U.S. & Canada)	unstable angina	MC, R, DB, PG	165 82 90 83 total 420 67/33; 32-76 yrs	Hirulog 0.02mg/kg/hr x 72 hr Hirulog 0.25mg/kg/hr x 72 hr Hirulog 0.5mg/kg/hr x 72 hr Hirulog 1.0mg/kg/hr x 72 hr	No statistically significant differences among groups in efficacy ("unsatisfactory outcome", defined as death, MI, ECG-documented failure of initial therapy (at least one episode of ischemic pain at rest >5min in duration with documented ECG changes)). No dose-response. Incidence of death and MI in the 0.02mg/kg/day group was higher than in the combined other three groups (10% at hospital discharge and 13% and 6 weeks vs. 3% at hospital discharge and 5% at 6 weeks). No difference among groups in adverse events.
C93-309	acute coronary syndromes: unstable angina or non-Q wave MI	MC, R, DB, PG comparison of Hirulog and heparin	68 65 total 133 58/42; 39-87 yrs	Hirulog 0.1mg/kg IV bolus + 0.25mg/kg/hr IV infusion x 12 hr to 7 days Heparin 70 U/kg IV bolus + 15 U/kg/hr IV infusion x 12 hr to 7 days	Planned for 5320 patients. Study terminated prematurely by sponsor for "business reasons". Death or MI: Hirulog, 3 pts (4%); heparin, 8 pts (12%) 3 Hirulog patients and 3 heparin patients experienced serious adverse events.
Uncontrolled Studies in Other Indications:					
C91-018 (Canada) interim study report	adjunctive therapy in patients undergoing thrombolytic therapy with [redacted] for acute MI	open-label, dose-ranging comparison of Hirulog and heparin	59 28 15 14 total 116 81/19; 25-79 yrs	(1) Hirulog 0.5mg/kg/hr x 12 hr + 0.1mg/kg/hr x 84 hr (2) Hirulog 1.0mg/kg/hr x 12 hr (3) Heparin 1000 U/hr x96 hr (4) Heparin 5000 U IV bolus + 1000 u/hr x 96 hr All pts received aspirin and [redacted]	TIMI grade 2 or 3 patency at 90 min: (1) 84%, (2) 79%, (3) 57% and (4) 54%. However, at day 4 patency was 80-100% in heparin groups and 80-96% in Hirulog groups. With both Hirulog and heparin the groups receiving infusion tended to do better than groups receiving only bolus. Rescue PTCA: (1) 8%, (2) 14%, (3) 53% and (4) 29%. Major bleeding events: Bleeding events requiring transfusion: Hirulog ,7%; heparin, 17%. Serious adverse events: Hirulog, 23%; heparin, 41% Deaths: (1) 3, (2) 1, (3) 2, (4) 0. Two Hirulog deaths possibly study drug related (cardiogenic shock and myocardial rupture)

C90-053 (Canada)	unstable angina	single-center, open-label, dose-escalating. (within patient)	15 60/40; 51-71 yrs	Hirulog 0.02mg/kg/hr x 30 min + 0.05mg/kg/hr x 30 min + 0.10mg/kg/hr x 30 min + 0.25 mg/kg/hr x 30 min + 0.5mg/kg/hr x 30 min	Dose-response relation of plasma levels and aPTT. Problems with blood-drawing mechanism (indwelling catheter) effect on thrombin generation. No major bleeding events. Most frequent adverse events: angina pectoris, headache, asthenia bradycardia. At F/U 8-32 days 53%, no cardiac events; 27%, angina; 13% recurrent unstable angina; 13% MI.
C90-054 (Canada)	unstable angina	single center, open-label, sequential dose-ranging	5 14 21 total 40 73/28; 33-77 yrs	(1) Hirulog 0.25mg/kg/hr up to 5 days (2) Hirulog 0.5mg/kg/hr up to 3 days (3) Hirulog 1.0mg/kg/hr up to 3 days	"Unsatisfactory outcome": (1) 2/5, 40% ;(2) 2/14, 14%; (3) 1/21, 5% Most common adverse events: headache, 40%, bradycardia, 23%; asthenia, 10%. Bleeding events: injection site hemorrhage, 10%; melena, 8%; eccymosis, 5%; hematuria, 3%.
C91-016 (U.S.)	unstable angina	2 centers, open-label	21 pts (all male) 100/0; 50-74 yrs	Hirulog 0.2mg/kg/hr x 5 days	Non-Q wave subendocardial MI shortly after dosing, 1; chest pain with ECG changes <24 hrs after start of infusion (underwent CABG), 1; died 6 days after dosing (ischemic bowel), 1; Q wave MI prior to dosing, 1; non-Q wave MI prior to dosing, 1. 3 pts with mild bleeding events: melena, 2; epistaxsis, 1.
C90-029	calf deep vein thrombosis	MC, open-label, dose-ranging	5 20 6 total 31 35/65; 42-88 yrs	Hirulog 1.0mg/kg SC injection Hirulog 1.0mg/kg SC injection, q12hr for 60 hrs Hirulog 0.6mg/kg IV infusion x 15 min	All regimens were ineffective No bleeding events.
C90-039	selected orthopedic surgical procedures	open-label, dose-ranging	18 68 49 28 59 total 222 41/59; 24-93 yrs	(1) Hirulog 0.3mg/kg bid SC injection up to 14 days (2) Hirulog 0.6mg/kg bid SC injection up to 14 days (3) Hirulog 1.0mg/kg bid x 3 days + 0.6mg/kg bid up to 11 days (4) Hirulog 1.0mg/kg bid x up to 14 days (5) Hirulog 1.0mg/kg tid x up to 14 days	Most frequent adverse events: fever (24%), eccymosis (20%), constipation (17%), pain (16%), nausea (14%), peripheral edema (11%), vesiculobulbous rash (10%), and hemorrhage (10%). Incidence of eccymosis: (1) 33%, (2) 30%, (3) 25%, (4) 7%, and (5) 5%. Four major and 1 minor bleed.

C93-312	heparin-induced thrombocytopenia (HIT) pts undergoing invasive intravascular procedure	MC, open-label, dose regimens varied by procedure done	19 53/47; 33-83 yrs	Hirulog 0.25mg/kg/hr x 72-96 hr Hirulog 2.5mg/kg/hr x 4 hr + 0.2mg/kg/hr x 20 hr Hirulog 2.5mg/kg/hr adjust dose to match target ACT	Anticoagulation was adequate for HIT/HITTS patients requiring PTCA, stent placement, cardiac catheterization, intraarterial balloon pump or vascular surgery. One pt with DVT developed PE and died. Three patients had major bleeds (intravascular puncture site hemorrhage, hemorrhage, and hematuria) Three pts discontinued because of adverse events, all involved bleeding.
C94-322	heparin-induced thrombocytopenia (HIT) pts undergoing invasive intravascular procedure	MC, open-label, dose regimens varied by procedure done	20	Hirulog	Outcomes of procedures: PTCA, 7/7 successful; CABG 3/4 improved, 1 died; peripheral angioplasty, 1 case, not successful technical problems;, coronary angioplasty, 1 pt stable; active HIT/HITTS (without procedure), 5/7 improved, 2 died.

reviewer's original table, based on information in sponsor's summary tables, NDA Vol. 1.49, pp. 202 through 260 and individual study reports

APPEARS THIS WAY
ON ORIGINAL

The pivotal clinical efficacy studies (C92-304-1 and C92-304-2) are presented and discussed in detail in the **CONTROLLED CLINICAL EFFICACY STUDIES** section of this review. The safety data from these studies is discussed in more detail in the **SAFETY ASSESSMENT** section of this review.

Human Pharmacology:
Clinical pharmacology studies consisted of PK/PD investigations in normal subjects and patients with renal impairment, bioequivalence studies of frozen and lyophilized formulations, and bioavailability of Hirulog given via the subcutaneous route. There were seven pharmacokinetic/pharmacodynamic (PK/PD) studies in healthy adult subjects (total of 163 subjects), one PK/PD study in 39 subjects (8 of whom were normal and 31 of whom had varying degrees of renal failure), and one safety study in 11 patients with renal failure on dialysis. There was one PK/PD study in 291 patients undergoing PTCA.

Based on the sponsor's reports, Hirulog was found to reliably inhibit coagulation as measured by activated partial thromboplastin time (aPTT) and activated coagulation time (ACT). The anticoagulant effect of Hirulog as measured by ACT was proportional to plasma levels of the drug and there was an approximately linear dose-response relationship with bolus doses ranging from 0.15 to 1.0mg/kg. Hirulog showed a plasma half-life of about 20-40 minutes and a volume of distribution consistent with distribution in plasma + interstitial water.

In subjects given Hirulog doses up to 0.6mg/kg as a 15 minute infusion, there was no drug detectable (<235ng/ml) in the plasma after 75 minutes in any subject. Clearance in normal subjects in these studies was about 3-7ml/min/kg. Subjects having moderate or worse renal failure (GFR <60ml/min) showed decreased clearance of the drug. Hirulog is thought to be cleared by a combination of proteolysis and renal mechanisms. It probably undergoes filtration at the glomerulus and some tubular reabsorption. After systemic proteolysis, the resulting amino acids are utilized by the body.

The 10 clinical pharmacology studies are described briefly in the table below. The pharmacokinetic and bioequivalence studies are being reviewed by FDA Biopharmaceutics.

Clinical Pharmacology Studies

Study	No. Subjects	Design	Treatments (bivalirudin and others)	Results
C90-010	72 healthy adult males, aged 18-36 yrs	single-blind, placebo controlled dose escalation	bivalirudin: 15 min IV infusion at 0.05, 0.075, 0.15, 0.3, 0.3mg/kg or placebo; bolus of 0.3mg/kg or placebo; sc injection of 0.3, 0.6, 1.0mg/kg or placebo; 12-24 hrs IV infusion at 0.3mg/kg/hr; intoraction with aspirin: 2 hr infusion of bivalirudin 0.6mg/kg/hr crossover with placebo or aspirin	Plasma AUC linearly related to bivalirudin dose. Antithrombotic effects linearly related to bivalirudin plasma AUC. Mean renal excretion ranged from 9.9% to 21.8% of total elimination. Concurrent aspirin did not affect PK or anti-thrombotic effects of bivalirudin. Half-life about 23 minutes after 15 minute infusion.
C91-125	16 healthy males, aged 21-29 yrs	double-blind, placebo-controlled, randomized, cross-over	sc injection of bivalirudin 12.5mg or 38.5mg in different solutions (saline, phosphate buffer, TRIS, NaOH)	sc injections only transiently caused minimal pain; phosphate buffer possibly associated with more pain; There was minor bruising at the injection site; No significant differences between vehicles; Physical examination and clinical laboratory studies did not reveal any toxicity.
C92-305	20 healthy adult males and females, aged 20-31 yrs	open-label, randomized, cross-over	Compared refrigerated and frozen formulations at 0.5mg/kg/hr X 4 hrs IV infusion	Formulations were bioequivalent with regard to AUC_{0-2a} and C_{max}. Frozen formulation had a longer T_{max}. More adverse events with the refrigerated formulation (especially much more nausea [60% vs. 10%]
C92-306	8 healthy adult females, aged 20-35 yrs	double-blind, randomized, placebo-controlled, crossover	refrigerated formulation, 0.5mg/kg/hr x 4 hrs or placebo	one subject with pre-existing arteriovenous malformation suffered an intracranial hemorrhage 18 days after dosing with bivalirudin. All subjects had some adverse event: nausea, vomiting and dizziness were most common with bivalirudin. Study stopped early
C93-310	15 healthy adult males, aged 22-35 yrs	randomized, double-blind, placebo-controlled, 3-period crossover	frozen and lyophylized formulations: 0.5mg/kg/hr x 4 hrs	Frozen and lyophilized formulations were bioequivalent with regard to AUC_{0-2a} and C_{max} No antibodies to bivalirudin on either initial exposure or rechallenge
C93-313	39 healthy males or females aged 21-73 yrs	open-label	? formulation; infusion 0.5mg/kg/hr x 4 hr	Tendency toward decreased bivalirudin clearance and increased pharmacologic effect (i.e., increased a PTT) in subjects with moderate and severe renal impairment; bivalirudin was dialyzable; few adverse events (most common, vasodilatation)
C93-316	20 healthy males aged 22-33 yrs	randomized, double-blind, 2-period crossover	pilot frozen formulation vs. commercial lyophilized formulation, infusion 0.5mg/kg/hr x 4 hrs	both formulations had similar aPTT-time curves; assay for bivalirudin failed due to drug being unstable in urine under the storage conditions used.
C93-317	12 healthy adult males aged 23-34 yrs	randomized, open-label 2-period crossover	bivalirudin 0.25mg/kg/hr x 4 hrs; heparin 15 U/kg/hr x 4 hrs	Antithrombotic effects of both heparin and bivalirudin appeared related to their respective plasma concentrations.

			one subject received heparin 35U/kg IV bolus followed by the heparin infusion	During switching from heparin to bivalirudin or vice versa there is a transient decrease in aPTT
C94-321	11 patients with renal failure on chronic dialysis, aged 30-73 yrs	open-label	4 different regimens of bolus (0.1-0.5mg/kg), followed by 4 hr infusion (0.5-2.0mg/kg/hr), followed by q8h sc dosing for 24 hrs (0.5-2.0mg/kg)	Bivalirudin was well-tolerated; APTT in these renal patients was predictably related to bivalirudin dose whether given by IV infusion, IV bolus or repeated sc injection.
C90-041	303 patients undergoing PTCA	open-label, dose-ranging, multicenter	6 different regimens of bolus (0.15-0.55mg/kg) followed by 4 hr infusion (0.6-2.5mg/kg/hr) followed by 0.2mg/kg/hr for up to 20 hrs post-PTCA	Anticoagulation (ACT, aPTT, PT) was related to drug dose; significant decrease in occurrence of unsuccessful angioplasty in pts at 3 higher dosing regimens as compared to 3 lower dosing regimens. AEs: 2 pts in 1mg/kg/hr group died (ventricular fibrillation and coronary artery disease); 1 AE withdrawal (transient ischemic attack); no discontinuations due to bleeding or peripheral vascular complications.

reviewer's original table, based on sponsor's table NDA Vol. 1.2, p. 146

APPEARS THIS WAY
ON ORIGINAL

Study C90-041 was an open-label, multicenter, dose-ranging study in patients undergoing PTCA which was used to estimate the study population size for the pivotal efficacy studies for the current application. In this study 291 male and female patients with >70% stenosis undergoing PTCA were treated with Hirulog using a bolus dose followed by a continuous infusion dose. Plasma drug levels were measured and ACT, aPTT, and PT were measured. Patients were evaluated for unsuccessful angioplasty defined by abrupt vessel closure (AVC) and complications. Study results are summarized in the following table:

Study C90-041: Summary of Study Results

Bolus (mg/kg) Infusion (mg/kg/hr)	0.15 0.6	0.25 1.0	0.35 1.4	0.45 1.8	0.55 2.2	1.00 2.5
Group	1	2	3	4	5	6
No. of patients dosed	57	50	45	73	54	12
No. of patients evaluated	52	44	41	70	51	12
Patients (%) achieving ACT >300sec	12%	26%	50%	72%	84%	100%
No. pts with unsuccessful angioplasty	3 (6%)	5 (11%)	6 (15%)	3 (4%)	2 (4%)	0 (0%)
Hirulog plasma concentrations (ng/ml)[a]						
mean	2860	6809	7096	12766	20871	17530
median	2826	4178	6599	12730	23825	17790
range						
n	8	8	6	4	5	12
aPTT (sec)[a]						
mean	101.3	118.2	133.9	137.5	137.3	-
median	98.1	117.0	124.0	136.0	138.5	-
range						
n	22	21	21	43	37	-
PT (sec)[a]						
mean	24.5	31.2	42.2	47.6	52.2	-
median	23.3	31.2	38.8	45.2	52.1	-
range						
n	20	24	20	43	37	-
TT (sec)[a]						
mean	81.2	244.5	177.7	97.4	86.4	-
median	100.0	258.5	129.0	100.0	88.9	-
range						
n	10	16	3	8	5	-
ACT (sec)[a]						
mean	228.1	264.6	322.3	315.5	324.6	315.1
median	228.0	276.0	317.0	313.0	323.5	310.5
range						
n	7	10	8	17	20	8

APPEARS THIS WAY
ON ORIGINAL

Adverse Events (no. patients):						
deaths	0	2	0	0	0	0
serious	2	1	0	2	1	0
discontinuations due to AE	1	0	0	0	0	0
bleeding events	13	21	20	35	26	5
major bleed	1	0	0	0	0	0
most frequent						
angina pectoris	13	19	19	32	16	4
IV puncture site hemorr.	7	17	13	24	19	3
back pain	16	1	5	17	9	2
eccymosis	3	1	9	10	10	0
nausea	10	3	2	2	4	2
headache	8	2	2	5	4	1
injection site pain	1	3	5	6	2	0
bradycardia	2	4	2	8	0	1
fever	4	4	5	0	3	0
hematuria	1	2	2	6	3	1
pain	1	3	3	5	1	2

* highest values at steady state (steady state defined as the IV infusion period between 100min after start of infusion and the end of the 4 hr infusion);

reviewer's table based on sponsor's tables, NDA Vol. 1.49, p. 149 and Vol. 1.66, p. 4 and 154 through 180

It should be noted that there was some adjustment in infusion rates in some patients based on ACT levels and the number and timing of coagulation studies was modified during the study. Hirulog was quantitated by an inhibitory enzyme immunoassay (EIA) that detects the drug through its ability to inhibit the binding of a specific monoclonal antibody to Hirulog bound to solid phase. Though collection of data was incomplete in this study, there appeared to be a dose-response with regard to the proportion of patients achieving the target ACT of >300 sec. Steady state ACT values of 300 or greater were pretty reliably achieved with Hirulog doses of at least 0.35mg/kg bolus followed by 1.4mg/kg/hr infusion and were associated with Hirulog plasma concentrations of about 7000ng/ml or greater.

The most frequent adverse events were angina, intravascular puncture site hemorrhage, back pain, and eccymosis. Two patients, both in the Hirulog 1mg/kg/hr group died, one of ventricular fibrillation during hospitalization and one after the study of coronary artery disease and cardiac failure. Six patients suffered serious adverse events, which included transient coronary artery occlusion, cardiac arrest, angina pectoris, myocardial ischemia, bradycardia and ventricular tachycardia. One patient in the 0.6mg/kg/hr group had a major bleed (required transfusion of 2 units of PRBC). One patient in the 1.4mg/kg/hr group had a retroperitoneal hemorrhage 6 days after receiving Hirulog.

To assess immunogenicity of Hirulog blood samples were tested for antibodies to Hirulog in 123 (42%) of patients in this study. Antibodies positive to Hirulog were detected in only 1 patient (1.8mg/kg/hr group).

The sponsor concluded that higher doses of Hirulog $\geq$1.8mg/kg/h are associated with a lower rate of AVC than the lower dose regimens and that Hirulog could safely be used for anticoagulation in patients undergoing PTCA. The sponsor selected the dosing regimen of 1.0mg/kg IV bolus followed by a 4 hour 2.5mg/kg/hr IV infusion for use in the pivotal Phase III studies.

CONTROLLED CLINICAL EFFICACY STUDIES:
Two identical controlled clinical efficacy trials were done (Study C92-304-1 and C-92-304-2). In addition, a subset of patients from these two studies were followed up with angiography 3-6 months after PTCA to assess restenosis (Study C93-319-P). These studies were done by Biogen prior to acquisition of the drug by the Medicines Company. These three studies are described and discussed below.

Description of Protocol:
Title: Protocol C92-304-2:A Multicenter, Double-Blind, Randomized Study to Compare the Safety and Efficacy of BG8967 with Heparin in Patients with Unstable Angina Undergoing Percutaneous Transluminal Coronary Angioplasty (PTCA)

A. **Objectives:** The primary objective of this study is stated as "to demonstrate the safety and efficacy of BG8967 [Hirulog, bivalirudin] in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) as a treatment for unstable angina, as compared with a control group of similar patients receiving heparin during PTCA."

Secondary objectives include (1) comparing the incidence of individual components of "procedural failure" in the two treatment groups and (2) comparing, from hospital discharge after PTCA to the 3 month and 6 month follow-up evaluations, the incidence of: cardiac death and "all-cause" death, myocardial infarction, symptom-necessitated revascularization (PTCA/CABG), ischemic pain requiring hospitalization, and evidence of restenosis.

B. **Study design:** This was planned as two identical randomized, double-blind, active control (heparin), multicenter, parallel group studies.

C. **Subjects:** These were to be up to 2000 patients aged 21 years or older having angiographic evidence of coronary artery disease with lesions suitable for PTCA and having unstable angina defined as a new onset of severe or accelerated angina or rest pain within the prior month developing in either the absence of an extracardiac condition or within two weeks after an acute myocardial infarction. Criteria for exclusion were: major illness (such as major infection, active severe liver disease, renal failure with serum creatinine $\geq$3.0mg/dl); APTT >200% of control; previous warfarin therapy causing a PT 15secs on the day of PTCA; treatment with lytic therapy for myocardial infarction, pulmonary embolus or deep venous thrombosis within 24 hrs of randomization; positive pregnancy test; body weight >110kg; planned multistage procedure; planned stent placement; lumbar puncture within past 7 days; severe trauma within the past 3 months; history of heparin-induced thrombocytopenia; known intolerance to aspirin; occlusive lesions in saphenous vein grafts that are over 3 yrs old, aorto-ostial lesions or diffuse lesions >20mm in length as target lesions; current or prior participation in any other study or current treatment with any other investigational drug or therapy within 7 days prior to study entry; previous participation in this study; treatment with dipyridamole on the day of PTCA (also, dipyridamole was not allowed during study drug administration); planned brachial approach; prior PTCA, atherectomy, or laser angioplasty within 4 weeks prior to randomization, or stent placement within 8 weeks prior to randomization.

D. **Study drug:** Patients were randomized to receive one of two treatments (heparin or Hirulog [BG8967]) during and following PTCA. The Hirulog dosing was based on the results of Study C90-041. In the original protocol the dosing regimens were to be:

- heparin - 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.
- BG8967 (Hirulog) - a bolus dose of 1.0mg/kg with continuous infusion of 2.5 mg/kg/hr.

However, in Amendment 1, made prior to enrollment of any patients, the treatment regimen for heparin was modified considerably based on discussions with investigators. The treatment regimens used are summarized in the sponsor's table below:

Treatment Regimens

Drug	Regimens
BG8967 [Hirulog]	
Infusion* (4 hrs)	2.5 mg/kg/hr
Bolus 1	1.0 mg/kg
Bolus 2	placebo
bolus 3	placebo
Infusion* (14-20 hrs)	0.2 mg/kg/hr
Heparin	
Infusion* (4 hrs)	15 U/kg/hr
Bolus 1	175 U/kg
Bolus 2	60 U/kg
Bolus 3	60 U/kg
Infusion* (14-24 hrs)	15 U/kg/hr

*For continuous infusion both heparin and Hirulog were administered at a rate of 50ml/hr.

sponsor's table modified, NDA Vol. 1.72, p. 276

Bolus 2 was given only if the 5 minute ACT was not $\geq$350 secs. Similarly Bolus 3 was given only if the ACT 5 minutes after Bolus 2 was not $\geq$350 secs. Note that for Hirulog boluses 2 and 3 were placebo to preserve the study blind.

All patients received aspirin (325mg in U.S. centers, 300mg in European centers) daily prior to and daily after the PTCA procedure. Patients who were receiving constant infusion heparin prior to PTCA were to have the heparin discontinued for at least 30 minutes prior to starting the study drug.

Hirulog was packaged in vials in an open label fashion and all study drug was prepared in syringes or infusion bags by an unblinded pharmacist. Heparin was supplied by each investigation site.

E. **Study plan:** Patients had medical history taken within a week prior to study entry. Within 72 hrs prior to study drug administration patients had physical examination, 12-lead ECG, clinical laboratory studies (CBC with differential, PT, APTT, AST, ALT, LDH, alkaiine phosphatase, BUN, serum creatinine, creatine phosphokinase (with MB band, if elevated), pregnancy test within 7 days of study entry for women of childbearing potential, and urinalysis). A flow chart showing the schedule of study procedures is shown below:

C92-304-P Study Flowchart

	Within 72 hrs of study entry	Within 1 hr prior to drug administration	Immediately prior to PTCA	During PTCA	After 13-17 PTCA	Within 24 hrs following discontinuation of infusion[9]	Between 7 and 14 days following discontinuation of infusion	3-month and 6-month follow-up
Medical history[1]	X							
Physical exam	X[2]					X[2]		
Vital signs	X	X[19]				X		
Pregnancy test[1] (if applicable)	X							
ECG (12-lead)	X[14]				X[8]	X[15]		
Hematology[3]	X					X		
Serum chemistry[4]	X					X		
CK[5]	X[5]				X[11]			
Urinalysis[6]	X					X		
ACT		X[7]	X[12]	X[13]		X[10]		
APTT, (PT only on screening)	X[16]					X[10]		
Arteriogram				X[17]				
Collection of plasma samples for determination of antibodies	X[18]						X[18]	
Off study patient assessment								X
Adverse study events, ischemic pain, concomitant therapy, bleeding	RECORD ALL DURING THE STUDY PERIOD							

[1] Within 7 days of study entry.
[2] Including weight (height at entry). Catheter insertion site is to be examined at off study evaluation.
[3] Hematology: CBC with differential and platelet count.
[4] Serum chemistry: AST (SGOT), ALT (SGPT), LDH, alkaline phosphatase, BUN and creatinine.
[5] CK-MB if total CK elevated. Pre-entry CK must be performed within 24 hrs of PTCA.
[6] Urinalysis: Includes protein, glucose, hemoglobin, and ketones (microscopic examination only if indicated).
[7] Just prior to study drug administration, preferably within 15 minutes prior to start of dosing.
[8] ECG: within one hour after PTCA and following every episode of ischemic pain at rest lasting at least 5 minutes. Also to be done 3 times, 8 hrs apart, following any episode of ischemic pain lasting at least 30 minutes or if significant changes are seen as compared to the pre-procedural ECG. For suspected ischemic events, a brief narrative must be provided. NOTE: If the ECG is normal at 8 and 16 hrs following the episode of pain, the third measurement is not required.
[9] Or prior to hospital discharge, whichever comes first.
[10] APTT or ACT may be drawn at time of (but not before) sheath removal. PT is not required.
[11] CK (CK-MB if total CK is elevated) should be recorded 3 times, 8 hours apart, following the PTCA procedure and following any episode of ischemic pain at rest lasting at least 30 minutes. If the CK is normal at 8 and 16 hours following the episode of pain, the third measurement is not required.
[12] ACT will be measured at least 5 minutes after the start of study drug infusion.
[13] ACT will be measured after 45 min of PTCA if procedure is still underway.
[14] ECG will be measured within 12 hrs prior to scheduled PTCA, preferably during a pain-free period.
[15] If the patient's condition precludes ECG measurement at this time, ECG will be performed within 24 hrs prior to discharge.
[16] For patients who have discontinued warfarin therapy prior to study start, PT must be measured on day of PTCA.
[17] Each lesion will be filmed in two projections before balloon dilatation, after each series of inflations with a balloon, and 10 minutes after guide wire removal.
[18] Plasma samples: Only collected for patients previously treated with BG8967 or previously enrolled in a blinded study of BG8967.
[19] Blood pressure and pulse, only.

sponsor's table, NDA Vol. 1.72, p. 265

On the day of study drug administration (Day 0), qualified patients were randomized to receive either heparin or BG8967 (bivalirudin). All patients were to receive 18 to 24 hours of anticoagulant therapy during the study. Vital signs were repeated within 1 hour prior to study drug administration and ACT was measured just prior to study drug administration. (Note: Patients who were on heparin prior to PTCA had heparin discontinued for at least 30 minutes prior to start of the study drug). The 4-hour intravenous infusion of study drug was begun at least 5 minutes prior to start of the PTCA and the bolus injection of study drug was given immediately after the start of the infusion. ACT was measured again at least 5 min after the start of the study drug infusion (just prior to PTCA). If ACT was <350sec, an additional bolus of study medication was given, consisting of 60 U/kg of heparin for the heparin patients and placebo for the BG8967 patients. ACT was measured again after 45 minutes and if ACT was still <350 sec a third bolus of heparin (or placebo) was given. After the first 4 hours of study drug infusion, additional infusion was given for another 14 to 20 hours. Heparin patients received heparin at the same rate as during the first 4 hours; BG8967 patients received bivalirudin at a dose of 0.2mg/kg/hr during this time.

PTCA was to be performed according to the physician's normal procedure with each set of balloon inflations being documented angiographically. The start of the procedure was defined as the insertion of the guide wire; the end of the procedure was defined as the time point when the guiding catheter is removed. A successful angioplasty procedure was defined as the ability to dilate the last lesion attempted such that the percent residual stenosis is not more than 50% by visual assessment.

At the end of the infusion period (about 18 to 24 hours after start of infusion), if the lesion was still felt to be unstable, patients were to receive open-label heparin therapy while awaiting subsequent treatment. Arterial and venous sheaths were to remain in place for at least 2 hours after discontinuation of study drug. ACT or APTT could be drawn after that time to determine whether drug effect had dissipated sufficiently to allow the catheter to be removed.

Any patient experiencing a major bleed or experiencing any "procedural failure" as defined above was to be withdrawn from the study. Patients also were to be withdrawn if the patient requested or if in the judgement of the principal investigator the patient was non-compliant or experienced adverse events or unforeseen risk due to other medical conditions.

All patients also received 325mg (300mg for European sites) aspirin daily prior to and after PTCA. Antianginal therapy was allowed as needed. Use of oral anticoagulants (other than aspirin) was prohibited during study drug administration. Dipyridamole was not allowed on the day of PTCA or during study drug administration. Patients requiring treatment with intracoronary urokinase or any lytic agent during study drug administration were classified as having met a study endpoint (i.e., require intervention).

Patients were considered to have completed the study upon reaching a study endpoint or at hospital discharge following successful PTCA.

F. **Efficacy parameters:** Efficacy endpoints were classified by a 5 member Morbidity and Mortality Classification Committee (MMCC), which consisted of 5 of the principal investigators. This committee was to receive on a bi-monthly basis case

reports forms, laboratory results, and other information on any patients who died, had a myocardial infarction, had rapid clinical deterioration (excluding ischemic pain) or had a hemorrhagic event. Sponsor's tables giving criteria for evaluating TIMI Grade Flow, assessment of bleeding, and relevant definitions are attached to this review as Appendix A. Based on this information (and with blinding intact) independent classification of the event would be made by two committee members for each event. If there was agreement between the two members, the classification would stand. If the two members disagreed, the case would be reviewed by all 5 of the committee members and the majority opinion would prevail. Classification would entail confirmation of the event, determination of whether the severity of the event met the pre-specified endpoint for the trial, subcategorization of the event according to specific etiologies, and subcategorization of the severity of the endpoint.

The primary efficacy endpoint for this study was specified as "procedural failure" which was defined as occurrence of one or more of the following:

- Death, occurring during hospitalization;
- Documented myocardial infarction occurring during hospitalization;
- Clinical deterioration of cardiac origin in patient's status during hospitalization, requiring revascularization or placement of an aortic counterpulsation balloon;
- Angiographic evidence of decreased coronary blood flow that requires use of an additional intervention such as emergency CABG, intracoronary urokinase, repeated balloon reinflation with a standard balloon or perfusion balloon catheter, or use of an investigational device (such as a stent) to treat abrupt vessel closure during hospitalization. (This amount of decreased coronary blood flow is described as "total or subtotal occlusion of the coronary vessel after attempted angioplasty as evidenced by deterioration of coronary blood flow to TIMI Grade 0 or 1 or at least a twofold increase in the minimal percent diameter stenosis, obtained after initially successful PTCA, or the emergence of impaired distal flow (defined by loss of at least one TIMI Grade of distal flow)."

The primary analyses were to be performed on an evaluable cohort and on an intent-to-treat cohort. The evaluable cohort was to consist of all patients randomized: who satisfied the inclusion/exclusion criteria; in whom the angioplasty catheter was inflated; in whom no atherectomy device or laser device was used; who did not have occlusive lesions in saphenous vein grafts that were over 3 years old, aorto-ostial lesions or diffuse lesions greater than 20mm in length as target lesions; and who did not have previous participation in this study. The intent-to-treat cohort was to consist of all patients randomized who received some study drug, whether or not PTCA was performed. [Note: Amendment 3 provided that in the ITT analysis all deaths (in or out of hospital) would be included].

Secondary efficacy endpoints include: comparison of the incidence of individual components of "procedural failure" between treatments; comparison of results of patients receiving study drug bivalirudin versus those who received heparin within one hour prior to study drug; comparison of results of patients receiving bivalirudin and those who received heparin more than one hour prior to study drug. Between treatment group comparisons from hospital discharge after PTCA to the 3-month and 6-month follow-ups will be made of: cardiac death and all-cause death;

myocardial infarction; symptom-necessitated coronary angiography; symptom necessitated revascularization; ischemic pain requiring rehospitalization; evidence of restenosis.

G. **Statistical methods:** The sample size for the studies was chosen, based on the results of the Phase 2 study of Hirulog in angioplasty (C90-041-P) to have 80% power to detect a 33% reduction in incidence of ischemic complications (the primary endpoints of procedural failure) for the Hirulog group relative to the heparin group.

The sponsor initially planned an interim analysis to be done when a total of 1600 evaluable patients had completed the treatment period. The incidence of "procedural failure" in each treatment group was to be determined in both studies individually and combined. In Study Amendment 3 (discussed below) the sponsor modified the procedure for the interim analysis such that the analysis was to be done when 1200 patients had been entered into each study and was to be done by estimating the overall event rate in each study without breaking the study blind. Resizing was to be done to achieve 80% power to detect a 33% reduction in the event rate using a 2-sided test at the 5% alpha level. (Resizing was to be used only to increase, not decrease, the sample size).

The primary efficacy analysis was done on two cohorts of patients: (1) evaluable patients - These are patients who were randomized, in whom no saphenous vein grafts more than 3 yrs old, no aorto-ostial lesions, and no diffuse lesions greater than 20mm in length were treated; and (2) intent-to-treat patients – all patients randomized who received some study drug whether or not angioplasty was performed.

The primary statistical comparisons were made using logistic regression models adjusting for center, age, multivessel disease, pre-procedural percent stenosis to adjust for any imbalances in prognostic factors.

Treatment groups were compared at baseline for demographic variables using descriptive statistics.

Because the sponsor's analysis of the study failed to show superiority of Hirulog over heparin with regard to the primary endpoint, the sponsor performed a post-hoc analysis to test for the clinical equivalence of Hirulog and heparin. For this analysis clinical equivalence with respect to the incidence of ischemic complications was determined using a tolerance level for the odds ratio (Hirulog/heparin) of 1.25 (a 25% increased risk for the Hirulog group). This tolerance level was specified by a committee of external clinical and statistical experts after study completion.

H. **Safety:** Subjects were to be evaluated for bleeding throughout the hospital stay. Bleeding was classified as "major": if it was clinically overt with a fall in hemoglobin level of 3g/dl or more; if it was clinically overt and led to a transfusion of 2 or more units of blood; if it was retroperitoneal; or if it was intracranial. Bleeding was classified as "minor" if it was clinically overt but not did not meet the other criteria for major bleed. If two or more bleeding events occurred simultaneously these were to be evaluated individually. Study drug was discontinued if major bleeding occurred.

Adverse events were to be recorded from 24 hrs prior to start of study drug and were to continue up to 24hrs after dosing is completed, or up to hospital discharge or up to time of another intervention, whichever came first. Events were graded as to severity, seriousness, possible relation to study drug administration, any action taken, and resolution of event.

Deaths or serious, life-threatening, unusual or unexpected adverse events were to be reported immediately by telephone to ClinTrials or the Biogen, Ltd. monitor and also reported to the institutional review board.

The Data Safety Monitoring Committee (DSMC) was to receive safety reports at 2-month intervals during the conduct of these two studies. The DSMC reviewed the safety data and advised the Operations Committee of the results of their review of the safety data and advised on safety and compliance matters and the future course of the protocol.

I. **Amendments:** The initial protocol was approved by the sponsor on December 14, 1992. Subsequently, there were 3 amendments to the protocol. Amendments 1 and 2 are dated January 29, 1993 and March 11, 1993, respectively, prior to initiation of patient enrollment into the trial and are reflected in the above description of the study. These amendments provided for a number of changes in the trial design, inclusion/exclusion criteria, study drug dosing, study procedures, and clarifications of some definitions. Also, it was stipulated that the protocol would be used for two independent studies which would then be analyzed both separately and combined; accordingly, total patients to be enrolled was increased to 4000 and these were to be randomly enrolled in one or the other of the two studies.

Amendment 3 is not dated. However, Protocol Version No. 4 (which reflects the changes made by this amendment) is dated November 12, 1993, seven months after initiation of patient enrollment into the study. The major changes made by this amendment include the following:

- clarified the process for determining which centers would be in each of the two studies. It stipulated that those centers which had already randomized at least one patient to treatment prior to this amendment were to be randomized to either study (C92-304-1 or C92-304-2). Additional centers were to be recruited into each study as needed (about 50 centers per study; about 40 patients per center) prior to the analysis of the adequacy of sample size at the interim analysis.

- modified the purpose and procedure for the interim analysis. The interim analysis was to be done to determine whether the sample size of the two studies is correct. It was planned to be done after 1200 patients had been enrolled in each of the two studies. The amendment states that the interim analysis is to be done in a blinded fashion using the overall event rate of the primary efficacy parameter and that no penalty need be imposed on the Type I error. [Ncte: According to FDA Biostatistics, (MRashid) no interim analysis was done];

- stipulated that the baseline ACT will be obtained preferably within 15 minutes prior to start of dosing and that the intravenous bolus injection of the study drug will be given within five minutes after the start of the infusion;

- added additional exclusion criteria: Treatment with dipyridamole on the day of PTCA (also, dipyridamole was not allowed during study drug administration); planned brachial approach; prior PTCA, atherectomy, or laser angioplasty within 4 weeks prior to randomization, or stent placement within 8 weeks prior to randomization; safety reports will be made to the Data Safety Monitoring Committee (DSMC) at two month intervals during the study;

- changed the randomization procedure so that those centers which had already randomized at least one patient to treatment prior to this amendment were to be randomized to either study (C92-304-1 or C92-304-2). Additional centers were to be recruited into each study as needed (about 50 centers per study; about 40 patients per center) prior to the analysis of the adequacy of sample size at the interim analysis;

- added a provision that the Data Safety Monitoring Committee would receive and review safety reports at 2-month intervals rather than at the completion of 1600 patients as previously specified;

- clarified the criteria for assessing bleeding;

- stipulated that in the ITT analysis all deaths (whether in or out of hospital would be counted;

- Revised the procedure for preparing the safety reports for the Data Safety Monitoring Committee.

Results Of Pivotal Efficacy Trials:

Study C92-304-1:

The Study Report for this trial is contained in NDA Vols. 1.71 through 1.111. The study protocol is included in NDA Vol. 1.72, pp. 161 through 312.

A. Investigators: This study was carried out from April 19, 1993 through April 17, 1995 by Biogen at 73 sites in 7 countries (64 U.S., 2 England, 2 France, 2 Netherlands, 1 Belgium, 1 Canada, 1 Switzerland). Investigators and study site numbers are listed below:

Study C92-304-1: Principal Investigators

Frank Aguirre, M.D. St. Louis University Medical Center St. Louis, MO	53	Michael Kutcher, M.D. Bowman Gray School of Medicine Wake Forest University Winston-Salem, NC	39
H. Vernon Anderson, M.D. University of Texas Medical School Houston, TX Hermann Hospital Houston, TX	119	James Madison, M.D./ Michael Mooney, M.D./ John Lesser, M.D. Abbott Northwestern Hospital Minneapolis, MN	42
Rodney Badger, M.D./Charles Dahl, M.D. Utah Valley Regional Medical Center Provo, UT	97	Peter Mahrer, M.D., F.A.C.C. Kaiser Foundation Hospital Los Angeles, CA	102
Jean-Pierre Bassand, M.D. Hospital Universitaire St. Jacques Besancon, France	75	James Mann, M.D. Wake Medical Center Raleigh, NC	14

James Bengtson, M.D., M.P.H. 30
St. Joseph Mercy Hospital
Ann Arbor, MI

Alain Bernard, M.D. 76
Cardio-Vascular Interventional Unit
Hartmann Centre
Neuilly, France

Alan Brenner, M.D. 55
Lakeland Regional Medical Center
Lakeland, FL

Bojan Cercek, M.D. 70
Cedars-Sinai Medical Center
Los Angeles, CA

Allen Ciuffo, M.D. 129
Sentara Norfolk General Hospital
Norfolk, VA

Patricia Cole, M.D. 57
Jewish Hospital
St. Louis, MO

Professor de Bono 26
Glenfeld General Hospital
Leicester, England

Michael Del Core, M.D. 96
The Cardiac Ctr., Creighton University
Omaha, NE

Antonio deLeon, M.D. 126
St. John Medical Center
Tulsa, OK

P. den Heijer, M.D. 139
University Hospital Groningen
The Netherlands

Ezra Deutsch, M.D. 03
Temple University Hospital
Philadelphia, PA

John Dieck, Jr., M.D./ Paul Tucker, M.D. 112
HCA South Austin Medical Center
Austin, TX

St. Daviud's Hospital
Austin, TX

Arthur Dodek, M.D. 33
St. Paul's Hospital
Vancouver, British Columbia

Frederick Feit, M.D./ Michael Attubato, M.D. 92
New York University School of Medicine
Tisch Hospital
New York, NY

Ted Feldman 108
University of Chicago
Chicago, IL

Peter Ganz, M.D. 06
Briogham and Women's Hospital
Boston, MA

Andrew McGinn, M.D. 106
North Memorial Medical Center
Minneapolis, MN

Raymond McKay, M.D./ Francis Kiernan, M.D. 130
Hartford Hospital
Hartford, CT

Thomas Meany, M.D. 124
University of Wisconsin Hospitals and Clinics
Madison, WI

Anthony Minisi, M.D. 16
McGuire V.A. Medical Center
Richmond, VA

Paul Moore, M.D. 95
Montgomery Cardiovascular Associates
Montgomery, AL

Joseph Muhlestein, M.D. 98
LDS Hospital
Salt Lake City, UT

Richard Myler, M.D. 63
San Francisco Heart Institute
Daly City, CA

Richard Nesto, M.D. 64
New England Deaconess Hospital
Boston, MA

Sebastian Palmeri, M.D. 73
Robert Wood Johnson Medical School
New Brunswick, NJ

Carl Pepine, M.D./Thomas Wargovich 18
University of Florida
J. H. Miller Health Center
Gainesville, FL

Jan Piessens, M.D. 141
University Hospital Gasthuisberg
Belgium

H. W. M. Plokker, Ph.D. 140
St. Antonius Hospital
The Netherlands

Richard M. Pomerantz, M.D. 103
University of Rochester Medical Center
Rochester, NY

LeRoy Rabbani, M.D. 93
Columbia Presbyterian Medical Center
New York, NY

M. Rothman, M.D. 49
The London Chest Hospital
London, United Kingdom

Gary Roubin, M.D./ Adam Cannon, M.D. 20
University of Alabama at Birmingham
Birmingham, AL

Kamran Ghalili, M.D. 58
Byran Memorial Hospital
Lincoln, NE

C. Michael Gibson, M.D. 29
Beth Israel Hospital
Boston, MA

Ginsburg, M.D. 86
Univ. of Colorado Health Science Center
Denver, CO

John Gordon, M.D. 133
Sharp Memorial Hospital
San Diego, CA

Paul Gordon, M.D. 121
The Miriam Hospital
Providence, RI

Edward Harlamert, M.D. 87
Community Hospital East
Indianapolis, IN

Vernon Hattori, M.D., F.A.C.C. 100
Daniel Freeman Memorial Hospital
Inglewood, CA

Timothy Henry, M.D. 35
Hennepin County Medical Center
Minneapolis, MN

John Hodgson, M.D./ John Strony, M.D. 08
University Hospitals of Cleveland
Cleveland, OH

Mun Hong, M.D./ Martin Leon, M.D. 90
Washington Hospital Center
Washington, D.C.

Kenneth Huber, M.D. 101
Mid America Heart Institute
St. Luke's Hospital
Kansas City, MO

Russell Ivanhoe, M.D./ A. Ralph Rodriguez, M.D. 37
Florkda Hospital
Orlando, FL

Alice Jacobs, M.D. 04
Boston University Medical Center
Boston, MA

Carl Jacobs, M.D. 120
Georgia Baptist Hosptial
Atlanta, GA

Kenneth Jutzy, M.D. 125
Loma Linda Univ. Medical Center
Loma Linda, CA

Carey Kimmelstiel, M.D. 113
Tufts New England Medical Center
Boston, MA

Spencer King, M.D. 61
Emory University Hospital
Atlanta, GA

James Kitchen, M.D. 11
Lankenau Medical Center
Wynnewood, PA

Nagui Sabri, M.D. 104
Lutheran General Hospital
Park Ridge, IL

Timothy Sanborn, M.D./ David Miller, M.D. 84
New York Hospital
New York, NY

Ian Sarembock, M.D., Ch.B., M.B. 43
University of Virginia
Charlottesville, VA

Yoseph Shalev, M.D. 111
University of Wisconsin Medical School
Milwaukee, WI

Thomas Shook, M.D. 66
Hospital of the Good Samaritan
Los Angeles, CA

Michael Stillabower, M.D. 94
Christiana Hospital
Newark, DE

Paul Urban, M.D. 135
Marion Community Hospital
Ocala, FL

Vladimir Vekstein, M.D. 107
Mt. Sinai Medical Center
Cleveland, OH

Jason Vita 91
West Roxbury, MA

Dr. Pierre Vogt 78
Chuv
Switzerland

Tom Wargovich, M.D. 18
J. Hillis Miller Health Care
Gainesville, FL

Mark Weston, M.D. 47
Tampa General Hospital
Tampa, FL

James Wilentz, M.D. 23
Lenox Hill Hospital
New York, NY

David Williams, M.D. 74
Rhode Island Hospital
Providence, RI

David Yardley, M.D. 68
St. Anthony Medical Center
Rockford, IL

B. Enrollment and Disposition of Patients: A total of 8166 patients were screened. Of these, 2318 patients (28%) were randomized. About 16% of patients screened and 13% of patients randomized suffered from post-MI angina (post-MI patients).

The sponsor's table shown below summarizes the enrollment of patients in this study:

Study C92-304-1: Patient Enrollment

	Number of patients (% of screened)		
	All Patients	Non-Post-MI Patients	Post-MI Patients*
Patients screened	8166	6072	1355
Patients not randomized	5848 (72)	4173 (69)	891 (66)
Reasons patients not randomized[1]			
Patient not eligible	3669 (45)	2507 (42)	487 (36)
Physician refused	499 (6)	380 (6)	95 (7)
Patient refused	811 (10)	610 (10)	162 (12)
Other	1114 (14)	853 (14)	183 (14)
Not specified	117 (1)	77 (1)	14 (1)
Patients randomized[1]	2318 (28)	1854 (31)	464 (34)
Patients who received any study drug[2]	2131 (92)	1722 (93)	409 (88)

* 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.
[1] percentages are relative to the total number of patients screened.
[2] Percentages are relative to the total number of patients randomized.

sponsor's table, NDA Vol. 1.71, p. 159

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.

A total of 187 patients (97 Hirulog and 90 heparin) were randomized but were not given study medication. The sponsor indicates that reasons these patients did not receive study medication were not recorded.

Patient disposition after randomization is shown in the table below:

Study C92-304-1: Patient Disposition[2]

	All Patients		Non-Post-MI Patients		Post-MI Patients	
	Hirulog	Heparin	Hirulog	Heparin	Hirulog	Heparin
Number of patients randomized	1168	1150				
Patients discontinued prior to receiving any study drug	97	90				
Patients receiving study drug	1071 (100)	1060 (100)	865 (100)	857 (100)	206 (100)	203 (100)
Discontinued due to adverse event	29 (2.7)	79 (7.4)	25 (2.9)	72 (8.4)	4 (1.9)	7 (3.4)
Discontinued due to endpoint[1]	135 (12.6)	140 (13.2)	115 (13.3)	119 (13.9)	20 (9.7)	21 (10.3)
Discontinued due to patient request	0	1 (0.1)	0	1 (0.1)	0	0
Discontinued due to physician request	20 (1.9)	11 (1.0)	19 (2.2)	7 (0.8)	1 (0.5)	4 (2.0)
Other	165 (15.4)	142 (13.4)	134 (15.5)	106 (12.4)	31 (15.0)	36 (17.7)
Completed infusion per protocol	722 (67.4)	687 (64.8)	572 (66.1)	552 (64.4)	150 (72.8)	135 (66.5)

[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. 1.71, pp. 160 and 161

Overall, about 66% of patients completed the study. About 3% of Hirulog patients and 7% of heparin patients were discontinued from the study prematurely due to adverse events. About 13% of patients in each treatment group were discontinued prematurely because of reaching a study endpoint. However, about 14% of patients discontinued prematurely because of unspecified "other" reasons.

C. **Intent-to-Treat Population:** The sponsor's Intent-to-Treat population included all 2131 patients who received study drug. The Hirulog patients were slightly older on average than the heparin patients in the overall and non-post-MI patient population (overall population: 62.3 yrs vs. 61.0 yrs, p=0.008; non-post-MI population: 62.6 yrs vs. 61.4 yrs, p=0.016). Otherwise, the treatment arms were well-balanced with regard to demographic features in the overall population and both the post-MI and non-post-MI strata. With regard to baseline cardiovascular features, the treatment groups were well-balanced in all regards. Demographic and baseline characteristics of the study population are summarized in the following table:

APPEARS THIS WAY
ON ORIGINAL

Study C92-304-1: 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=1071	N=1060	N=865	N=857	N=206	N=203
Age (yrs)						
mean	62.3	61.0	62.6	61.4	60.8	59.4
median	63	62	64	62	62	60
range	29-88	26-88	29-88	31-86	30-87	26-88
<65	576 (54)	624 (59)	460 (53)	492 (57)	116 (56)	132 (65)
>65	495 (46)	436 (41)	405 (47)	365 (43)	90 (44)	71 (35)
Gender						
male	731 (68)	698 (66)	582 (67)	566 (66)	149 (72)	132 (65)
female	340 (32)	362 (34)	283 (33)	291 (34)	57 (28)	71 (35)
Race						
white	964 (90)	964 (91)	783 (91)	789 (92)	181 (88)	175 (86)
black	67 (6)	58 (5)	51 (6)	40 (5)	16 (8)	18 (9)
Hispanic	20 (2)	19 (2)	16 (2)	11 (1)	4 (2)	8 (4)
other	20 (2)	19 (2)	15 (2)	17 (2)	5 (2)	2 (1)
Days since most recent MI						
mean	746.0	778.6	1307.1	1296.4	41.9	25.6
median	44	52	806	568	6	6
range	0-12373	0-10920	2-12373	0-10920	0-5846	0-2253
Heparin administration within 1 hr of study drug						
yes	234 (22)	234 (22)	169 (20)	171 (20)	65 (32)	63 (31)
no	837 (78)	826 (78)	696 (80)	686 (80)	141 (68)	140 (69)
Baseline ACT (sec)						
<200	970 (91)	949 (90)	784 (91)	776 (91)	186 (90)	173 (85)
200-300	55 (5)	59 (6)	46 (5)	43 (5)	9 (4)	16 (8)
>300-350	12 (1)	9 (<1)	10 (1)	3 (<1)	2 (<1)	6 (3)
>350	7 (<1)	8 (<1)	5 (<1)	6 (<1)	2 (2)	2 (<1)
unknown	27 (3)	35 (3)	20 (2)	29 (3)	7 (3)	6 (3)
Number of vessels with >50% stenosis (pre-PTCA)[1]						
1	535 (50)	556 (52)	427 (49)	459 (54)	108 (52)	97 (48)
2	355 (33)	325 (31)	284 (33)	251 (29)	71 (34)	74 (36)
3	176 (16)	169 (16)	149 (17)	140 (16)	27 (13)	29 (14)
Location of most severe lesion						
proximal RCA	517 (48)	504 (48)	418 (48)	402 (47)	99 (48)	102 (50)
mid RCA	418 (39)	419 (40)	330 (38)	345 (40)	88 (43)	74 (36)
distal RCA	117 (11)	115 (11)	99 (11)	93 (11)	18 (9)	22 (11)
Complexity of most severe lesion[2]						
A	344 (32)	372 (35)	287 (33)	303 (35)	57 (28)	69 (34)
B	580 (54)	528 (50)	475 (55)	440 (51)	105 (51)	88 (43)
C	128 (12)	138 (13)	85 (10)	97 (11)	43 (21)	41 (20)
Thrombus present in most severe lesion						
Yes	26 (2)	23 (2)	17 (2)	17 (2)	9 (4)	6 (3)
No	1026 (96)	1015 (96)	830 (96)	823 (96)	196 (95)	192 (95)
Percent stenosis in most severe lesion						
<50%	74 (7)	78 (7)	64 (7)	65 (8)	10 (5)	13 (6)
>50%	978 (91)	960 (91)	783 (91)	775 (90)	195 (95)	185 (91)
TIMI grade flow in most severe lesion[3]						
0	28 (3)	40 (4)	24 (3)	29 (3)	4 (2)	11 (5)
1	11 (1)	11 (1)	10 (1)	10 (1)	1 (<1)	1 (<1)
2	27 (3)	13 (1)	18 (1)	9 (1)	9 (4)	4 (<1)
3	986 (92)	974 (92)	795 (92)	792 (92)	191 (93)	182 (90)
Previous cardiovascular disease:						
prior coronary angioplasty	270 (25)	264 (25)	250 (29)	242 (28)	20 (10)	22 (11)
prior coronary bypass surgery	101 (9)	106 (10)	93 (11)	99 (12)	8 (4)	7 (3)
myocardial infarction	476 (44)	509 (48)	276 (32)	311 (36)	200 (97)	198 (98)
Patients with angina						
New onset of severe or accelerated angina; no rest pain	365 (34)	354 (33)	314 (36)	309 (36)	51 (25)	45 (22)
Angina at rest within part month	704 (66)	700 (66)	550 (64)	543 (63)	154 (75)	157 (77)

[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. 1.71, pp. 173 through 188

Most patients had one or more coronary risk factors. About 57% of all patients had history of hypertension and 25% were current cigarette smokers. Forty-eight percent had elevated cholesterol requiring treatment and 21% had diabetes mellitus. Smoking was more common in the post-MI group (about 36% 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 24% 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.

About 40% of patients had prior use of cardiovascular medications. (Most common medications were nitrates (23% of patients), calcium channel blockers (7% of patients), beta-blockers (5% of patients), and antiarrhythmics (3% of patients). Three percent of patients had prior use of aspirin. During the study about 72% of patients were on calcium channel blockers, 50% were on beta-blockers, 18% were on antiarrhythmics, and 15% were on angiotensin-converting enzyme inhibitors. Ninety-nine percent of patients were on aspirin during the study. The most common prior non-cardiac medications were lidocaine (56% of patients), diazepam (51% of patients), diphenhydramine (45% of patients) and midazolam (22% of patients). During the study the most common non-cardiac medications used were oxygen (53% of patients), morphine (44% of patients), iohexol (30% of patients) and [redacted] (30% of patients).

D. **Evaluable Population:** One hundred sixty patients who received study medication were excluded from the evaluable population. These included 138 non-post-MI patients (71 Hirulog; 67 heparin) and 22 post-MI patients (10 Hirulog; 12 heparin). These patients and reasons for exclusion are summarized in the following table:

Study C92-304-1: 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	1071	1060	865	857	206	203
Total patients excluded from evaluable population:	81[c]	79[d]	71[c]	67[d]	10	12
Angioplasty catheter not inflated	30	32	26	24	4	8
Atherectomy or laser device utilized	15	13	15	11	0	2
Saphenous vein grafts >3yrs old[a]	0	2	0	1	0	1
Not a candidate for PTCA	0	0	0	0	0	0
Did not have unstable angina	0	2	0	2	0	0
Saphenous vein grafts >3yrs old treated[b]	38	32	32	31	6	1

[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] Two patients (#004/0525, non-post-MI), an 81yo man, and (#017/0519, non-post-MI), a 62yo woman, had saphenous vein graft over 3 yrs old treated with atherectomy or laser device;
[d] Two patients (#053/0510, non-post-MI), a 45yo man, and (#130/0514, non-post-MI), a 54yo man, had saphenous vein graft over 3 yrs old treated with atherectomy or laser device.

reviewer's original table, based on data from sponsor's table, NDA Vol.1.77, pp. 327 through 340

E. **Efficacy Analysis:** Among the 2131 patients who were randomized and received study medication, 167 patients (77 Hirulog, 90 heparin) experienced procedural failure during the study. The efficacy results for the total population and for the non-post-MI and the post-MI populations are summarized in the following table:

Study C92-304-1: 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	1071	1060		865	857		206	203	
Overall procedural failure	77 (7)	90 (8)	0.253	67 (8)	72 (8)	0.629	10 (5)	18 (9)	0.104
Death, MI or revascularization	61 (6)	73 (7)	0.236	54 (6)	60 (7)	0.500	7 (3)	13 (6)	0.178
Death or MI	23 (2)	28 (3)	0.467	23 (3)	21 (2)	0.769	0	7 (3)	0.001**
Death	3 (<1)	1 (<1)	0.302	3 (<1)	0	0.026*	0	1 (<1)	0.283
Documented MI not present at enrollment	21 (2)	28 (3)	0.312	21 (2)	21 (2)	0.992	0	7 (3)	0.001**
Revascularization	49 (5)	65 (6)	0.100	42 (5)	55 (6)	0.144	7 (3)	10 (5)	0.483
Established AVC	22 (2)	29 (3)	0.325	19 (2)	22 (3)	0.700	3 (1)	7 (3)	0.150
Impending AVC	8 (< 1)	9 (<1)	0.829	6 (<1)	6 (<1)	0.913	2 (<1)	3 (1)	0.607

* 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 ECG [redacted] Lab using protocol-specified criteria.
Note: AVC was determined by ([redacted] laboratory using protocol-specified criteria.
Note: Percentages are relative to the total number of patients in each treatment group.

sponsor's table, NDA Vol. 1.71, p. 189

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). Death was determined by the individual investigator at that site. Clinical deterioration of cardiac origin requiring revascularization was determined by the investigator and specified on the CRF. Myocardial infarction (MI) not present at enrollment, identified by the ECG [redacted] was defined as defined as any of the following: definite Q-wave MI, definite non-Q-wave MI, and definite MI with new left bundle branch block (LBBB). Established and impending AVC were identified by the [redacted] In the overall population, there were no statistically significant differences between treatment groups in the proportions of patients having any of the primary or secondary efficacy endpoints. The only statistically significant differences seen were more deaths in the Hirulog group as compared to the heparin group among the non-post-MI patients (3/865 Hirulog patients vs., 0/857 heparin patients ($p=0.026$) and in the post-MI stratum a higher incidence of "death or MI" in the heparin group as compared to the Hirulog group (7/203 heparin vs. 0/206 Hirulog patients, $p=0.001$) and a higher incidence of documented MI not present at enrollment in the heparin group as compared to the Hirulog group (7/203 heparin vs. 0/206 Hirulog patients, $p=0.001$). Multiple comparisons were not taken into account in these comparisons of the treatment groups.

Some features of the study drug administration (dose, duration, etc.) for the intent-to-treat population are summarized in the following table:

Study C92-304-1: Summary of Study Drug Administration (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
Total Duration of Study Drug Administration (hrs)[a]:						
mean	15.7	15.4	15.4	15.3	16.6	15.9
median	18.1	18.1	18.1	18.1	18.2	18.2
range	0.1-31.8	0.1-36.0	0.1-31.8	0.1-36.0	0.3-24.3	0.2-24.3
Total Amount of Study Drug Administered (mg/kg [Hirulog] or U/kg [heparin])						
mean	12.44	423.35	12.27	420.59	13.16	435.01
median	13.8	448.5	13.8	447.5	13.8	458.5
range	[redacted]					
Bolus Doses of Drug (number of patients, (%))[b]:						
Bolus #1	1069 (>99)	1059 (>99)	863 (>99)	856 (>99)	206 (100)	203 (100)
Bolus #2	555 (52)	321 (30)	450 (52)	250 (29)	106 (51)	71 (35)
Bolus #3	302 (28)	98(9)	245 (28)	76 (9)	57 (28)	22 (11)
Number of patients with study drug dose reduction	27 (3)	116 (11)	22 (3)	100 (12)	5 (2)	16 (8)
Reason study drug reduced[c]:						
bleeding event	16 (1)	86 (8)	13 (2)	73 (9)	3 (1)	13 (6)
adverse event	1 (<1)	4 (<1)	0	4 (<1)	1 (<1)	0
other	11 (1)	27 (3)	9 (1)	24 (3)	2 (<1)	3 (1)

[a] Interruptions to study drug administration were not included in the duration totals.

[b] Patients in the Hirulog group received 1mg/kg Hirulog in first bolus and placebo in second and third bolus doses. Patients in the heparin group received 175U/kg heparin in first bolus and 60U/kg heparin in the second and third bolus doses. The second bolus was to be administered after 5 min ACT if ACT<350 sec. The third bolus was to be administered at 45 min ACT if ACT <350 sec and PTCA was ongoing.

[c] Patients may have more than 1 reason for study drug dose reduction.

from sponsor's tables, NDA Vol. 1.71, pp. 217 through 221

F. **Six-Month Follow-up:** Follow-up data was available for about 98% of all patients who received any study drug in this study. The follow-up data are summarized in the following table:

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	1071	1060		865	857		206	203	
Total number of patients with 6-month follow-up data	1047 (98)	1031 (97)	N.D.	848 (98)	834 (97)	N.D.	199 (97)	197 (97)	N.D.
Any Event	529 (51)	535 (52)		447 (53)	442 (53)		82 (41)	91 (46)	
Death, MI or revascularization	194 (19)	199 (19)		168 (20)	168 (20)		26 (13)	31 (16)	
Death or MI	32 (3)	33 (3)		29 (3)	23 (3)		3 (2)	10 (5)	
Death	17 (2)	11 (1)		16 (2)	6 (<1)		1 (<1)	5 (3)	
MI	19 (2)	22 (2)		16 (2)	17 (2)		3 (2)	5 (3)	
Revascularization	176 (17)	181 (18)		152 (18)	157 (19)		24 (12)	24 (12)	
PTCA	127 (12)	123 (12)		108 (13)	106 (13)		19 (10)	17 (9)	
CABG	65 (5)	75 (7)		58 (7)	66 (8)		7 (4)	9 (5)	
Angina requiring hospitalization	224 (21)	234 (23)		186 (22)	201 (24)		38 (19)	33 (17)	
Angina	496 (47)	499 (48)		416 (49)	419 (50)		80 (40)	80 (41)	
Coronary angiography	228 (22)	268 (26)		195 (23)	227 (27)		33 (17)	41 (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. 1.71, p. 209