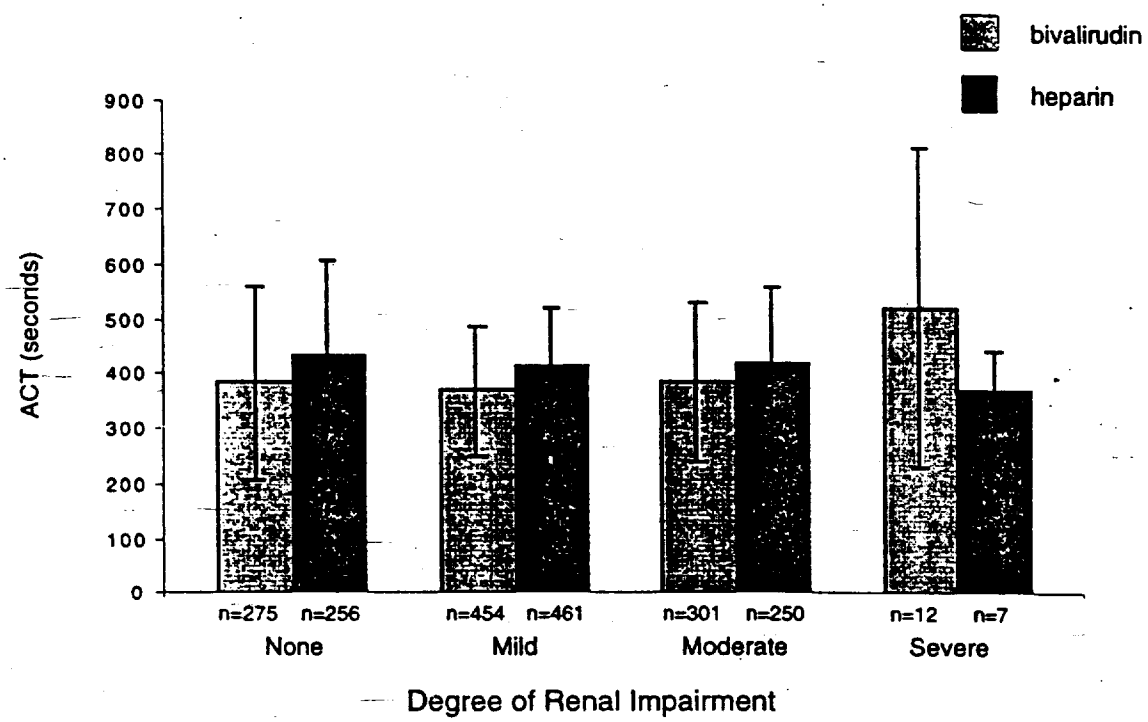
Figure 4. Mean (±S.D) 45 Minute ACT (seconds) by GFR Category. Controlled Studies C92-304-1 and C92-304-2 Combined



Using data from the Phase 3 studies, each of the following factors was evaluated with respect to its ability to account for the variability of bleeding rates in bivalirudin-treated patients: GFR category (normal, mild renal impairment, moderate renal impairment, and severe renal impairment), gender (male, female), and age (<65, ≥65). A total of 1914 bivalirudin-treated patients with non-missing data were included in this analysis. For each covariate and combination of covariates a coefficient of variation (R^2) was calculated using a logistic regression model and the method proposed by Nagelkerke [8]. Using this method R^2 is scaled to have a maximum value of one, corresponding to the case where all variability is accounted for by covariates in the logistic model. Results from this analysis are presented in Table 3.

Table 3: Bleeding Covariate Analysis

EXPLANATORY VARIABLE(S)	R^2
GFR category	0.054
Gender	0.021
Age	0.027
GFR category and gender	0.063
GFR category and gender	0.057
Age and Sex	0.042
GFR category, gender, and age	0.066

Results from this analysis indicate that GFR category accounts for twice the variability in bleeding as either sex or age (R^2=0.054 versus 0.021 and 0.027, respectively). In addition, GFR category alone accounts for nearly all of the variability accounted for by all three covariates together (R^2=0.054 for GFR category versus 0.066 for GFR category, gender, and age).

However, GFR category does not fully account for the increased bleeding risk in females. Adjusting for GFR category and age, females are significantly more likely to experience a bleeding event than males, as evidenced by an odds ratio (95%CI) of 1.75 (1.02, 3.02). Adjusting for GFR category and sex, patients 65 years of age and older are not significantly more likely to have a bleeding event than patients less than 65 years of age [odds ratio (95% CI) of 1.49(0.77, 2.88)].

Rationale for Bivalirudin Dosing Recommendations in Renal Impairment

The evidence from the pharmacokinetic and pharmacodynamic data in renal impairment indicates that there is a need to reduce the dose of bivalirudin in renal impairment. Elderly patients have reduced glomerular filtration rates and dose reduction is also indicated for elderly patients on the basis of their GFR. Total bivalirudin clearance will be reduced in direct proportion to the degree of renal impairment. For a drug with a narrow therapeutic indication this would necessitate dose reductions in direct proportion to the degree of renal impairment. For bivalirudin the pharmacodynamic data in renal impairment and the analysis of incidence of major hemorrhage *versus* calculated GFR in the phase III data provides evidence that dose reduction is only required in patients with moderate and severe degrees of renal impairment (GFR<60ml/mm, <1ml/sec). In these patients the same loading dose should be used, followed by reduction in the maintenance infusion dose according to the degree of renal impairment.

Similarly for elderly patients (>65 years of age) GFR should be estimated using the Cookcroft and Gault formula and the maintenance dose reduced on the basis of the calculated GFR, if this is less than 60ml/mm or 1ml/se glomerular filtration rate can be estimated using the Cookcroft and Gault formula:

$$GFR(ml/s) = \frac{(140\text{-age}) \times \text{weight (kg)}}{48869 \times \text{plasma creatinine (mmol/L)}} \quad (\times 0.85 \text{ for females})$$

Dose Adjustment Proposal to be Included in Label

Renal Function (GFR mL/min)	Initial Bolus	Infusion for 4-hours
Normal renal function ≥90 ml/min	1mg/kg	2.5mg/kg/h
Mild renal impairment 60-90 ml/min	1mg/kg	2.5mg/kg/h
Moderate renal impairment 30-59 ml/min	1mg/kg	1.25 mg/kg/h
Severe renal impairment 10-29 ml/min	1mg/kg	0.5 mg/kg/h
Dialysis dependent patients (monitor ACT)	1mg/kg	0.25 mg/kg/h

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Attachment 4

Figure 3: Maximum BG8967 concentrations and steady-state aPTT measurements (C90-041)

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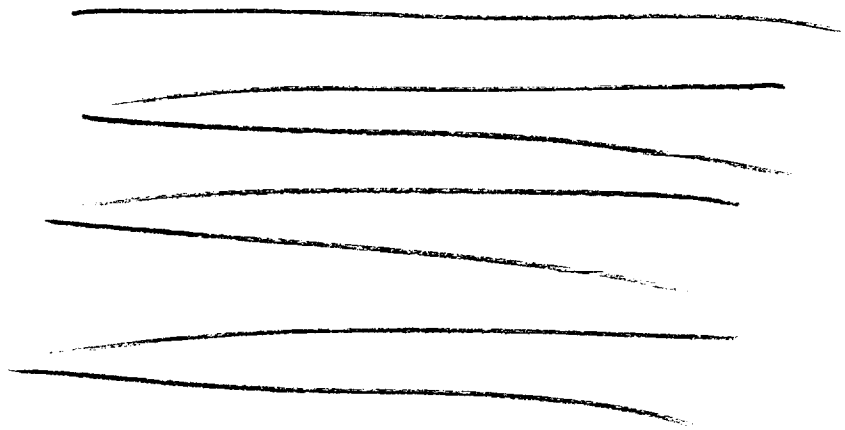

Similar aPTT E_{max} values are obtained for Hirulog doses of 0.6 mg/kg/h and 1 mg/kg/h while plasma bivalirudin mean Cmax value for the 1 mg/kg/h dose was approximately twice the value for the 0.6 mg/kg/h dose.

Even with the uncertainties related to the specificity of the ELISA assay, these results strongly support that bivalirudin concentrations are needed for accurate comparison of Hirulog formulations and that aPTT measurements are not suitable to link the data from C93-310 and C93-316. Significant differences in aPTT measurements are reported due to differences in commercially available aPTT reagents (6-9).

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4. STUDY PATIENTS

- Eleven patients are reported in this interim analysis; 8 males and 3 females.
- All patients entered in the study received study drug (bivalirudin) and so these patients comprise the Study Population.
- For the GFR subcategories, there is one patient with moderate renal impairment, 5 patients with mild renal impairment and 5 patients with normal renal function.
- All patients received study drug (bivalirudin bolus and infusions). However one patient was under-dosed by 17% and one patient had their infusion start 44 minutes after their bolus dose.
- Protocol deviations were infrequent and did not affect the study results. The most common deviation was missing a blood sample (not taken) or an ACT test (failure of the Hemochron® or insufficient sample).

Individual patient data and patient demographics are given in tables 1 and 2 respectively.

4.1 Patient Data.

Patients were pre-stratified according to their sex and calculated GFR. Once a potential patient for the study was identified the Study Project Manager was contacted to check that a patient of a given sex and GFR was required from that site.

It was planned for each centre to recruit 15 patients; 7 or 8 males and 7 or 8 females; 5 patients with normal renal function (i.e. calculated GFR 90+ ml/min), 5 patients with moderate renal impairment (i.e. calculated GFR 60-89 ml/min) and 5 patients with mild renal impairment (i.e. calculated GFR 30-59 ml/min). Within each of the two categories of renal impairment, 3 sub-categories were defined to ensure a spread of GFR values within each group. Ideally no more than one patient per sub-category per centre per sex was required. The goal was to obtain a spread of calculated GFR values for each gender.

Table 1 summarises the patient entry information.

Table 1
Individual Patient Data

Green Lane Hospital patients: 401–407; Flinders Medical Centre patients: 501-504;

Renal function category	Calculated GFR (ml/min)	Age at Study Entry (years)	Sex	Patient Number
Normal	151.3	55.2	M	405
Normal	114.5	52.0	M	403
Normal	104.3	56.3	M	404
Normal	103.0	51.8	F	407
Normal	95.6	55.5	M	503
Mild impairment	86.1	50.4	M	402
Mild impairment	85.4	67.5	M	501
Mild impairment	76.3	65.9	M	502
Mild impairment	71.5	70.0	M	401
Mild impairment	64.8	65.4	F	406
Moderate impairment	36.3	77.7	F	504

4.2 Patient Demographics

- Demographics of the two patient populations are similar.

Table 2 outlines the demographic characteristics of the study population:

Table 2

Demographic Characteristics (Study Population)

Characteristic	All Patients N (%)	Green Lane Site N (%)	Flinders Site N (%)
Number of patients	11 (100%)	7 (64%)	4 (36%)
Gender: Male	8 (73%)	5(71%)	3 (75%)
Female	3 (27%)	2(29%)	1 (25%)
GFR (ml/min):			
30-59	1 (9%)	0 (0%)	1 (25%)
60-89	5 (45%)	3 (43%)	2 (50%)
90+	5 (45%)	4 (57%)	1 (25%)
Mean age (years)	60.7	57.3	66.6
Mean systolic/diastolic BP (mmHg)	126.5/75.0	127.1/75.7	125.0/73.3
Mean weight (kg)	82.4	89.1	70.5

One patient (405) had Non-Insulin Dependent Diabetes Mellitus.

4.3 Protocol Deviations

- Two patients at the Green Lane Hospital site did not receive their treatment as per the protocol. One patient (401) had a 17% reduction in the dose of bivalirudin in their infusion, due to a counting error in the number of bivalirudin vials added to their infusion bag (i.e. 5 vials of bivalirudin were added to the infusion bag instead of 6). Another patient (407) received their bolus dose but the infusion was not started until 44 minutes later.
- For ACT tests, three patients had one timepoint where either a blood sample was not taken or the corresponding ACT test result was unavailable. The ACT tests failed either because the sample taken was too small or the [redacted] battery was too low. However, due to the number of other timepoints available, the pharmacodynamic calculations were not affected.

5. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

5.1 Mean Bivalirudin Plasma Concentrations and ACTs during Infusions of 2.5 mg/kg/hr and 0.5 mg/kg/hr

- Plasma concentrations were similar for patients with normal renal function and those with mild renal impairment, achieving steady state of 15-20 µg/ml at the 2.5 mg/kg/hr dose and 4-6 µg/ml at the 0.5 mg/kg/hr dose.in most patients The patient with moderate renal impairment had higher plasma concentrations of bivalirudin, with a steady state of around 30-40µg/ml at the 2.5mg/kg/hr dose, and 13-16 µg/ml at the 0.5 mg/kg/hr dose.

- ACT values were similar in all groups, achieving a steady state of around 350 seconds with the 2.5 mg/kg/hr dose and around 220 seconds during the 0.5 mg/kg/hr infusion.

Mean bivalirudin concentrations and ACT values at each of the timepoints measured are given for patients with normal renal function (Table 3), mild renal impairment (Table 4) and moderate renal impairment (Table 5) and presented graphically in Figures 1, 2 (kinetics) and 3 (dynamics). Individual patient plasma concentrations are given numerically and graphically in Appendix Ia and II. Individual ACT values are given in Appendix III and IV. Individual bivalirudin urine concentrations are given in Appendix Ib.

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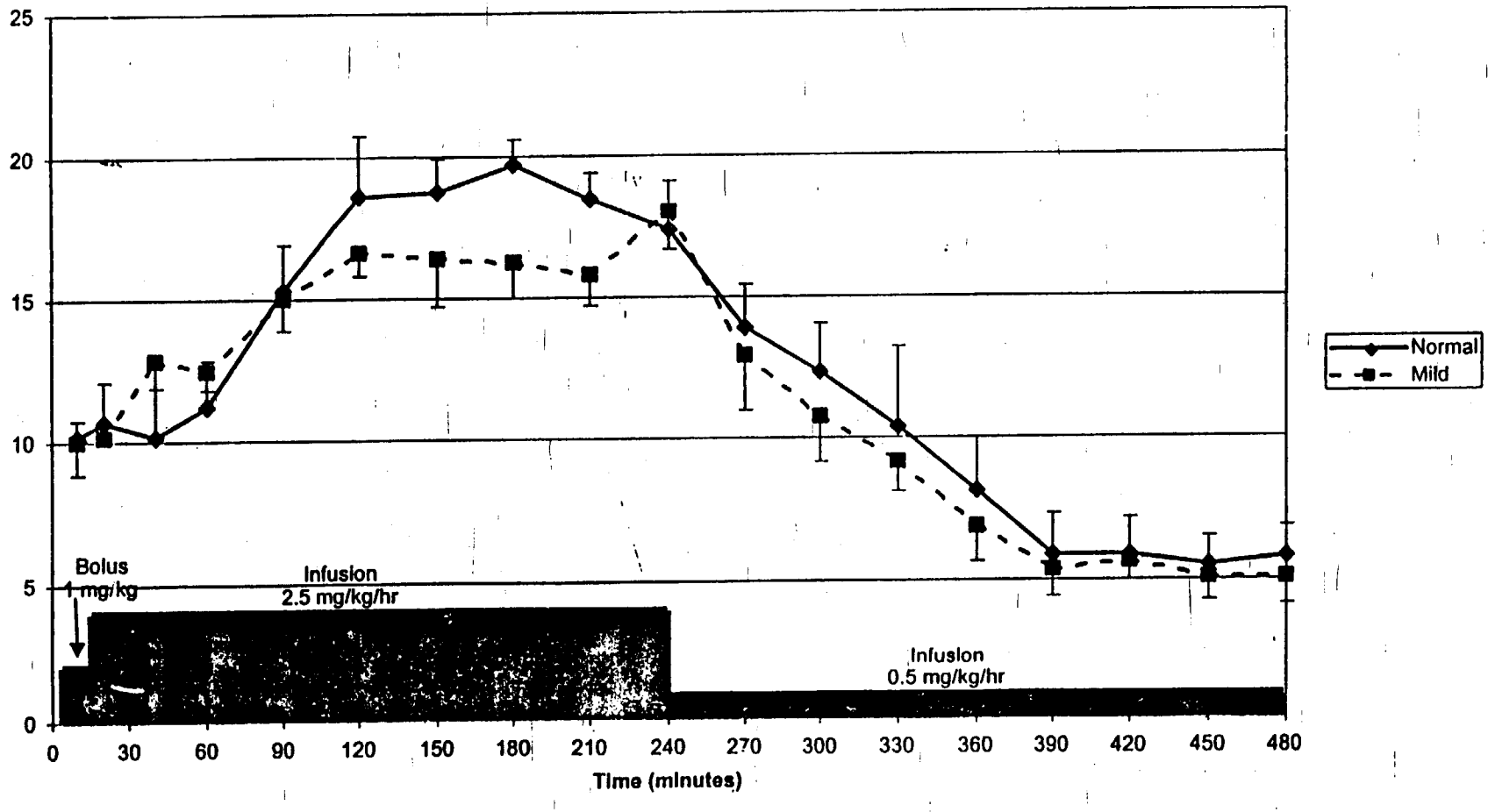
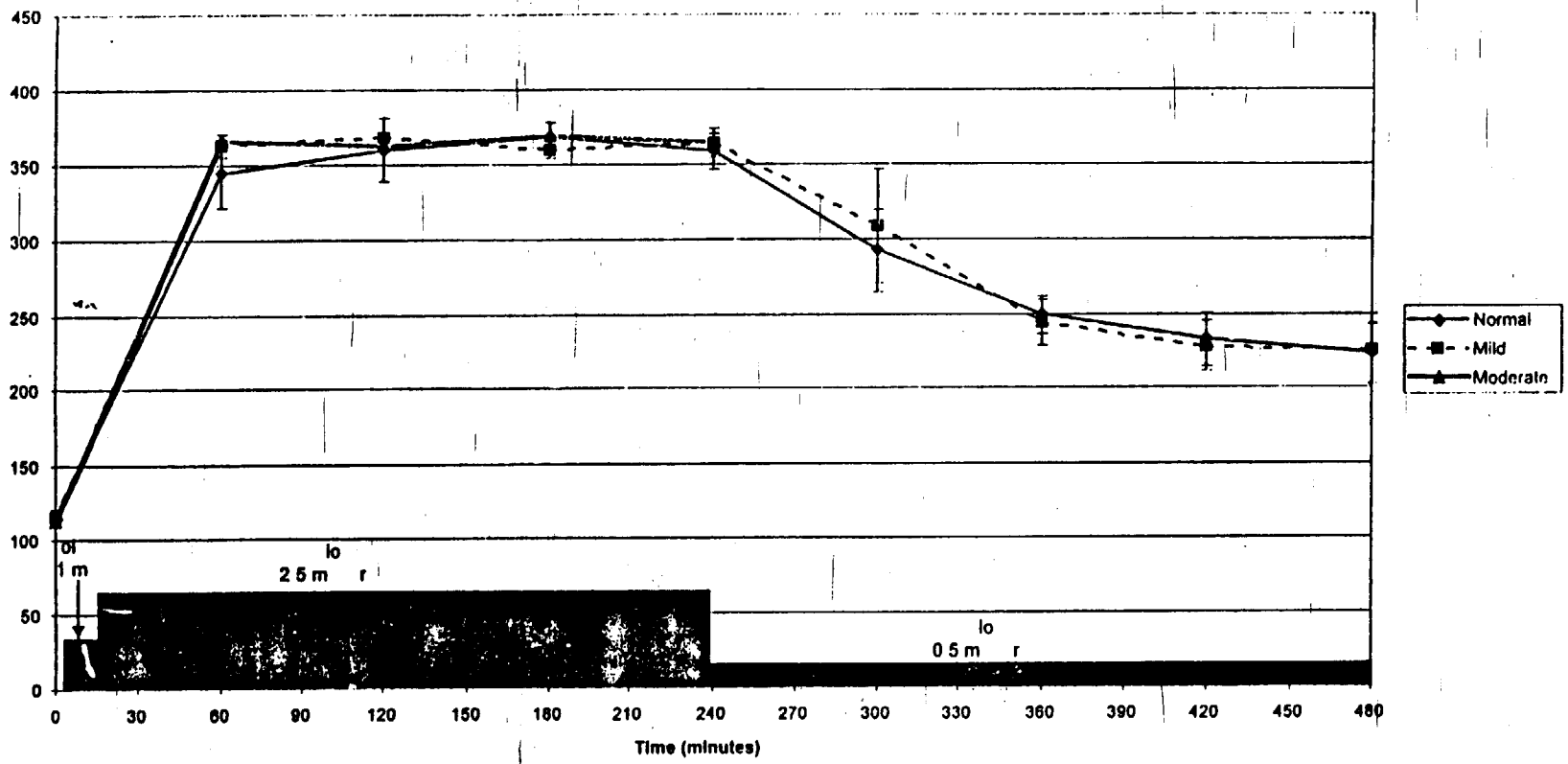
Fig.1 - Mean (+/- SD) Plasma Bivalirudin Concentrations for Patients with Normal Mild Renal Function



1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Fig.3 - Mean (+/-SD) Plasma ACT Values for Patients with Normal, Mild & Moderate Renal Function



10 page(s) of revised draft labeling has been redacted from this portion of the review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-873
Hirulog® (Bivalirudin) Injection

Submission Date:
December 29, 1997
January 31, 1998
February 25, 1998
March 25, 1998
May 11, 1998

NOV 19 1998

Sponsor: **Quintiles for Medicines Company, Cambridge, Massachusetts**

Reviewer: Arzu Selen, Ph.D.

Type of submission: Original NDA

Code: 1S

BACKGROUND

Hirulog, originally developed by Biogen, Cambridge, MA (patented March 23, 1993) was acquired by the Medicines Company, Cambridge, MA, in March 1997. Following a meeting with the Agency in August 1997, the Sponsor submitted the Hirulog NDA, NDA 20-873, on December 29.

Hirulog (bivaluridin, BG8967) is a completely synthetic 20 amino acid peptide, claimed to be a direct and specific thrombin inhibitor. The Sponsor has proposed use of Hirulog as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) and has evaluated Hirulog against heparin in this patient population. The Sponsor also claims an advantage over heparin that Hirulog can be used in patients with heparin-associated thrombocytopenia (HAT) and heparin-induced thrombocytopenia and thrombosis (HITTS). In the NDA, the Sponsor claims better safety but similar efficacy profile to heparin. However, as heparin is not an approved treatment for anticoagulation in PTCA patients, safe and effective use of Hirulog for this indication was identified as one of the topics to be discussed at the advisory committee meeting.

This review is based on the clinical pharmacology and biopharmaceutics information submitted in the NDA and the subsequent 4 amendments made by the Sponsor in January, February, March and May 1998. In addition, in this review, occasional references are made to the Sponsor's recent amendment dated October 19, 1998 to identify the additional information provided by the Sponsor before the Advisory Committee Meeting took place on October 23rd 1998. This most recent amendment provides responses to some of the questions that were raised earlier and also informs of ongoing work by the Sponsor. However, even with this amendment there are still outstanding issues that may be addressed in the future if the Sponsor would wish to continue development of bivalirudin. Because of unresolved issues, an adequate assessment of the clinical pharmacology and biopharmaceutics information of the Hirulog NDA 20-873 can not be made in this review. Nevertheless, the available information is presented in order to provide a scope of the submission and also to indicate the areas identified for further assessment.

Following the advisory committee meeting on October 23rd, 1998, the clinical division has decided not to approve bivalirudin based on lack of sufficient safety and efficacy data.

Since submission of the Hirulog NDA 20-873, five amendments were made by the Sponsor (January 31, February 25, March 25, May 11, and October 19, 1998).

The first amendment, dated January 31, 1998, was submitted by the Sponsor prior to communication of the comments raised during the NDA 45 Day Filing Review. This amendment consisted of CMC stability data and a diskette of individual plasma bivalirudin concentrations obtained from Hirulog pharmacokinetic studies (C90-010, C90-041, C91-016, C92-305, C92-306, C93-310, C93-313, and C93-317). In this amendment, it was indicated that Study C91-016 included on the diskette had not been included in the NDA. As there is no other information supporting the data provided for C91-016, and because of pending assay method related questions (including non-specificity of the assay), a review of this data file is not included in this review.

The items noted during the 45-Day Filing Review of the Hirulog NDA included issues related to analytical methods, calculation of pharmacokinetic parameters, data interpretation (such as period and formulation interaction), evaluation of drug-drug interactions, and dose-adjustment in renal impairment (recommended in summary documents but not reflected in the proposed package insert). These items were communicated to the Sponsor in the FDA letter dated February 11, 1998.

In Sponsor's February 25, 1998 response, some of these items were addressed while other items were acknowledged to be outstanding by the Sponsor. The FDA's response to this amendment was on March 17, 1998.

On March 24, 1998, the Sponsor provided via fax a copy of a published article as the proposed study design for the in vitro drug-drug interaction study (1) in response to one of the items raised in the FDA letter dated February 11, 1998. The proposed study design was considered acceptable and this was communicated to Ms. Julieann DuBeau, the Consumer Safety Officer, on March 24, 1998.

The Sponsor submitted a third amendment, dated March 25, 1998, to address some of the remaining issues raised in the FDA February 11, 1998 letter.

Finally, a paper copy of the in vitro metabolism article, sent to the Agency via fax on March 24, 1998 was submitted by the Sponsor and included in the May 11, 1998 Amendment.

Third and fourth FDA letters (dated May 19 and June 15, 1998) were sent to the Sponsor listing outstanding items from the previous Agency letters and requesting additional information and clarification for items that were noted during continued review of the Hirulog NDA 20-873. Some of these items such as clarification of specificity of bivalirudin assay and information regarding assay method and sample handling had been requested from the Sponsor in the FDA February 11, 1998 letter.

The Sponsor's recent amendment, dated October 19, 1998, addresses most of the issues that were raised in earlier FDA letters although in this amendment the Sponsor has indicated that additional work is ongoing to address bivalirudin assay related issues.

SYNOPSIS

Hirulog, a 20 amino acid peptide is similar to hirudin as it inhibits thrombin-mediated or associated processes or functions, however, unlike hirudin, binding of bivalirudin to thrombin is reversible and its binding affinity to thrombin is 1000-fold lower than that of hirudin (2). Hirudin, a polypeptide derived

from medicinal leech, hirudo medicinalis, inhibits thrombin by forming a complex which is more effective in inhibiting clot-bound thrombin in vitro than the heparin-AT III complex (3). As an anticoagulant, modeled after hirudin, an advantage of Hirulog over heparin is claimed to be its ability to act on free and fibrin-bound thrombin (4).

The proposed dosage form of Hirulog is 250 mg lyophilized powder for solution. In the proposed package insert, Hirulog is recommended to be administered to patients as a 4 h infusion, at an infusion rate of 2.5 mg/kg/h with a 1 mg/kg iv bolus dose administered immediately after initiation of the infusion. After completion of the 4 h infusion period, Hirulog infusion could be extended at 0.2 mg/kg/h rate for up to 20 h, as clinically warranted. The Sponsor has indicated that this recommendation is based on data from 2161 Hirulog-treated patients studied in two randomized, double-blind studies comparing Hirulog and heparin in a total of 4312 patients undergoing PTCA for treatment of unstable angina. The Sponsor's analyses of these efficacy trials show that Hirulog has a similar efficacy but better safety profile than heparin. However, at the Advisory Committee Meeting, higher bleeding events observed with heparin were attributed to aggressive use of heparin in these patients while acknowledging that heparin has not been approved for this indication.

A review of the summary documents (Sections 3 and 6 of the NDA and the supporting clinical pharmacology study reports) shows that pharmacokinetic and/or pharmacodynamic data were obtained from a small number of studies over a dose range mostly lower than the recommended clinical dose. Although a limited number of pharmacokinetic studies were conducted, efforts were made to study bivalirudin pharmacokinetics in patients with renal impairment and also in volunteers undergoing dialysis.

The specificity of the assay method for bivalirudin has not been adequately addressed by the Sponsor, and as a result the pharmacokinetic parameters provided by the Sponsor can not be considered meaningful. Furthermore, in the recent amendment (October 19, 1998), the Sponsor has included a 1994 dated draft analytical report (Attachment 8 of the Amendment) where an attempt was made to characterize bivalirudin metabolites in plasma by [redacted] MS. As indicated in this report, bivalirudin could be determined in the plasma samples of the volunteers. In addition, bivalirudin related 4 to 7 analytes were detected in the postdose plasma samples and structures were proposed for 4 of these analytes. The identity of these metabolites could not be confirmed in this study, possibly due to lack of reference materials at that time. Based on this draft report, the Sponsor could utilize the existing LC/MS assay method for accurate characterization of bivalirudin concentration and pharmacokinetic parameters.

In the following section, a summary of the available information on Hirulog and key points for future considerations are presented.

Absorption:

As Hirulog is an injectable formulation for iv administration, bioavailability issues are not anticipated. A subcutaneous formulation has been evaluated in earlier studies but is not included in the current NDA submission plan.

Distribution:

Distribution volume of bivalirudin is stated to be small (approximately 0.2 L/kg, Volume 1.002 page 137). This appears to be consistent with its protein-binding characteristics, as bivalirudin is indicated not to bind to plasma proteins except thrombin.

Since assay specificity has not been demonstrated and information in the recent amendment (October 19, 1998) indicates the likelihood of circulating metabolites of bivalirudin in plasma (which may also be detected by the ELISA assay used in this submission), the bivalirudin distribution volume, as reported in this review, is considered to be descriptive and not suitable for labeling purposes.

Metabolism and Elimination:

Metabolism or routes of excretion of bivalirudin were not studied in humans. However, literature articles are included in Section 6 describing catabolism of proteins (5). It is conceivable that as a peptide, bivalirudin is most likely proteolytically metabolized to individual amino acids. In preclinical studies, it was noted that a significant portion (approx. 80%) of the radiolabeled bivalirudin was recovered within the first day of dosing (P90-035, P8967-93-13).

It is claimed that bivalirudin is rapidly and completely excreted with estimated elimination half-life ($t_{1/2}$) values ranging from 20 to 40 minutes (Volume 1.038, page 7). Accumulation of bivalirudin is not expected with the recommended dosing regimen even though bivalirudin clearances were lower in patients than those seen in healthy volunteers. Lower clearance of bivalirudin in patients may be due to the health status of the patients. However, it is also possible that this observation may reflect dose-dependency in bivaluridin clearance as the doses studied in volunteers were lower than the clinical dose and this may warrant further exploration if higher doses of Hirulog are intended for clinical use.

A specific assay should be used for quantitation of bivalirudin and this would allow characterization of disposition of bivalirudin. The LC/MS assay method provided in the October 19, 1998 amendment (Attachment 8) could be utilized for accurate quantitation of bivalirudin concentrations and thereby, accurate assessment of bivalirudin elimination half-lives and clearances and furthermore, this method or its optimized version may be able to provide information on circulating putative bivalirudin metabolites (4 to 7 bivalirudin related analytes) in plasma.

Drug-Drug Interaction Studies:

In response to the FDA request, in March 1998, the Sponsor proposed an in vitro metabolism study to explore the potential of possible drug interactions with bivalirudin. A draft report of the results of this study are included in the October 19, 1998 amendment. A preliminary review of this report shows that bivalirudin is unlikely to inhibit the activity of the major human p450 enzymes.

The Sponsor has claimed that no adverse events were observed in PTCA patients in the efficacy trials that could suggest drug-drug interactions, particularly with chronic prophylactic anticoagulants, thrombolytics, and other agents.

In the clinical trials, C92-304-1 and C92-304-2, the sponsor reports a higher incidence of major bleeding events in patients receiving heparin, warfarin, and other thrombolytics in addition to Hirulog than patients who received Hirulog alone. However, the Sponsor has also claimed that occurrence of major bleeding events were lower in patients randomized to Hirulog (including patients with concomittant thrombolytic administration) than the patients randomized to heparin. The further assessment of this claim is expected to be in the safety assessment of the medical review of this NDA.

In addition, potential of interaction of bivalirudin was studied with heparin and aspirin, respectively, in two

studies, C93-317 and C90-010. Lack of an appreciable effect of aspirin on bivalirudin pharmacokinetics and pharmacodynamics is reported. Again uncertainty regarding analytical methods preclude further assessment of these results. When switching from continuous iv infusion of heparin to bivalirudin, a transient increase in activated partial thromboplastin times (aPTT), and from bivalirudin to heparin a transient decrease in aPTT was observed (and is reflected in the proposed package insert).

Patients with renal impairment and patients undergoing dialysis:

Slower clearance of Hirulog in patients with moderate to severe impairment (GFR < 60 ml/min) was noted and this is also stated in the proposed package insert. In addition, a dose-adjustment recommendation is made for patients undergoing dialysis (Study C93-313).

As communicated to the Sponsor earlier, dose-adjustment recommended for patients with severe and moderate renal impairment in the summary documents needs to be also reflected in the package insert.

In study C93-313, 0.5 mg/kg/h doses of bivalirudin were administered for 4 h to normal subjects and patients with varying degrees of renal impairment. The recalculated "clearance" values of bivalirudin is approximately 4-5 ml/min/kg in subjects with GFR values equal to or greater than 60 ml/min. Whereas in subjects with GFR values between 30 to 59 ml/min and GFR values less than 30 ml/min, the mean (SD) bivalirudin "clearance" values were 2.41 (1.47) and 1.11 (0.46) ml/min/kg, respectively. In dialysis patients, the mean (SD) bivalirudin "clearance" values were 0.83 (0.44) ml/min/kg for patients off-dialysis and 1.81 (0.63) ml/min/kg for patients on-dialysis.

In response to the Agency's request, the Sponsor has proposed a dosing scheme for bivalirudin in Attachment 6 of the October 19, 1998 Amendment. The proposed bivalirudin dose for the patients with GFR values equal to or greater than 60 ml/min is 2.5 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose) and for patients with GFR values 30 ml/min to 59 ml/min, the proposed bivalirudin dose is 1.25 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose). And for patients with GFR values less than 30 ml/min, the proposed bivalirudin dose is 0.75 mg/kg/h for 4 h (plus 1 mg/kg iv bolus dose). It is important to note that even the proposed adjusted dosing scheme is based on doses higher than the dose evaluated in the renal impairment study, C93-313, and is based on approximations. Furthermore, unresolved analytical issues such as use of a nonspecific assay, precludes an accurate determination of clearance values. The proposed dosing scheme is considered unacceptable and needs to be further studied in a relevant clinical setting following quantitation of bivalirudin by a specific assay.

<u>Bioequivalence of Hirulog Formulations</u>

Specificity of the bivalirudin assay as well as other analytical method related issues need to be resolved prior to further evaluation of bioequivalence of Hirulog formulations. In this NDA, the Sponsor refers to two studies (C93-310 and C93-316) to link the clinical trial formulations to the proposed injectable product. Because of the peptide nature of the product, it is possible that differences in manufacturing processes may result in Hirulog batches with different antithrombin activity. As a result, to ensure that the clinical trial formulations and formulations tested in Phase I and preclinical studies were comparable and linked, during early development of Hirulog, Hirulog formulations were compared in clinical bioavailability/bioequivalence studies. The major assumption in these studies was that comparable plasma bivalirudin concentrations, as determined by an ELISA assay, reflected the antithrombin activity of these Hirulog products.

In Study C93-310, the pilot scale frozen Hirulog formulation (Lot 67Z01S), used in efficacy trials was compared against the pilot scale synthesis, lyophilized Hirulog formulation (Lot 67Z04S).

In Study C93-316, intended to be the pivotal bioequivalence study, the two formulations of Hirulog, pilot scale frozen formulation (Lot 67A04Z) and commercial scale synthesis lyophilized formulation (Lot 67A02Q) were compared. However, because of lack of temperature control, the Sponsor has indicated that bivalirudin concentrations could not be measured in Study C93-316. Subsequently, the Sponsor has amended the report for Study C93-310 to reflect the reanalysis of data (calculation of 90% confidence intervals for bioequivalence assessment) in order to support the bioequivalence of the lyophilized formulation (commercial scale synthesis) to the frozen formulation (pilot scale).

The Sponsor has proposed linking of the two studies C93-310 and C93-316 based on aPTT measurements. However, as discussed in the main review section, bivalirudin concentrations are needed for accurate comparison of Hirulog formulations and that aPTT measurements are not suitable to link the data from C93-310 and C93-316 to support comparability of Hirulog products.

Furthermore, during review of this NDA, the Sponsor has also indicated that they can no longer manufacture Hirulog injectable product according to the method submitted in this NDA and they need to modify the manufacturing method. As a result, if the Sponsor decides to continue with development of bivalirudin, and will not use the data in this NDA for future submission(s), then the bioequivalence assessments or comparisons made in this NDA are not pertinent for future considerations.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Divisions of Pharmaceutical Evaluation II and III have reviewed the clinical pharmacology and biopharmaceutics information of the Hirulog NDA 20-873 and the responses from ([redacted] dated February 25, March 25, and May 11, 1998. The information needed for complete review of Hirulog NDA 20-873, requested in several FDA letters dated February, March and June 1998 were not available during review of this NDA. Although some of the responses to the questions raised by the Agency have been provided in the Sponsor's October 19, 1998 submission, in the same amendment, the Sponsor has also indicated that they will continue to work on assay related issues.

If the Sponsor decides to continue development of the Hirulog injectable product, then it is important that the Sponsor discusses the issues raised below with the Office of Clinical Pharmacology and Biopharmaceutics. The primary issues that were noted during review of this NDA are the following:

- The Sponsor has reported that clearance of bivalirudin in patients with renal impairment is significantly lower than that of the patients with normal renal function and had proposed dose-adjustment in these patients in summary documents but not in the proposed package insert. In response to the Agency's request, in the October 19, 1998 Amendment, the Sponsor has proposed a "questionable" dosing scheme for patients with renal impairment and for patients undergoing dialysis. The dosing scheme proposed by the Sponsor is considered questionable because it refers to doses not even tested in the renal impairment study and furthermore, issues related to non-specificity of the ELISA assay have not been resolved. As a result, accuracy of bivalirudin clearance estimates is unknown. The Sponsor has indicated that they will be continuing to work on assay related issues.

  If the Sponsor decides to continue development of bivalirudin, it is recommended that the Sponsor

conducts a pharmacokinetic/pharmacodynamic study in patients with renal impairment, and use a specific assay (such as the LC/MS method used in the October 1998 Amendment) for quantitation of bivalirudin. This study may be conducted according to the OCPB guidance (Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling) and per guidance, it will include control group subjects as well as patients with renal impairment. Use of a specific bivalirudin assay in this study will allow accurate assessment of bivalirudin pharmacokinetic parameters and appropriate dosing recommendation for this patient population.

The renal impairment study may be conducted in control group of volunteers (both male and female) receiving 0.5 mg/kg/h dose of bivalirudin for 4 h and PTCA patients with normal and impaired renal function receiving the following bivalirudin doses for 4 h. The recommended Hirulog doses for the PTCA patients would be 2.5 mg/kg/h, 2.0 mg/kg/h, 1.0 mg/kg/h and 0.5 mg/kg/h for the patients with normal renal function (GFR > 80 ml/min), mild renal impairment (GFR: 50-80 ml/min), moderate renal impairment (GFR: 30-50 ml/min) and severe renal impairment (GFR < 30 ml/min), respectively. In addition to collection of blood at specified times, all urines voided during the study must also be collected. The Sponsor is encouraged to discuss the renal impairment study protocol with the Agency.

- In addition, the draft report on LC/MS analysis of bivalirudin metabolites in plasma included in the October 1998 Amendment, suggests that additional metabolite isolation and identification efforts may be warranted.

/S/ Nov. 17/1998

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/S/ 11/18/98

RD initialed by
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/S/ 11/19/98

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cc: NDA 20-873, HFD-180 (Talarico, DuBeau),
HFD-870 (Chen, Hunt, Lee), HFD-880 (Selen), HFD-850 (Lesko)
HFD-340 (Viswanathan), Central Document Room (Barbara Murphy)

Table of Contents:

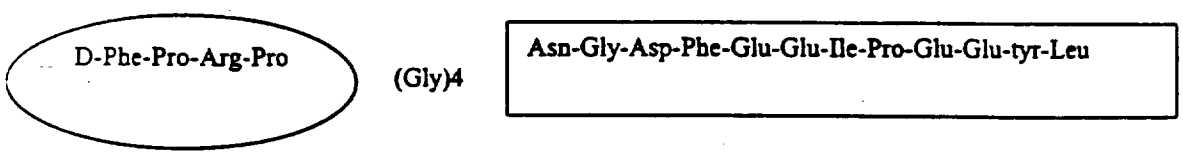
1. Drug substance and mechanism of action

Hirulog (bivaluridin, BG8967) is a completely synthetic polypeptide with the following sequence of amino acids:
D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-aspargyl-glycyl-L aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-tyrosyl-L-leucine trifluoracetate (salt) hydrate. Molecular weight of bivalirudin is 2180.19 daltons. It is claimed to be readily soluble in water.

Hirulog was developed as a direct-acting AT III independent thrombin inhibitor.

Hirulog and hirugen were developed after hirudin, a 65 amino acid polypeptide. Hirudin binds to thrombin at its catalytic site and also at its anion binding exosite by an anionic tail fragment. Hirugen, a dodecapeptide comprising of amino acid residues of 53 to 64 of the C-terminal region of hirudin, exerts its antithrombin activity by its interaction with the anion binding exosite of thrombin (5). The binding of hirugen to thrombin blocks fibrinogenolysis without affecting Factor V activation or the amidolytic activity of the enzyme. The advantage of Hirulog over hirugen is that it has a tetrapeptide region, D-Phe-Pro-Arg-Pro, that interacts with the catalytic site of thrombin. This tetrapeptide is linked to a fragment identical to the anion binding tail fragment of hirudin by a polyglycyl linker. As a result, bivalirudin achieves inhibition of both the fibrinogenolytic and amidolytic activities.

The amino acid sequence of bivalirudin is as follows:



Catalytic site Binding region **Hirudin tail fragment**

Bivalirudin has been shown to have activity on free and clot-bound thrombin (4).

2. Drug product formulation and manufacturing considerations

The formulation history of Hirulog and a list of studies conducted to evaluate Hirulog formulations are provided in Attachment A.

The IND [redacted] was for a frozen preparation using mannitol-phosphate buffer formulation which was originally prepared as a 1 ml product and later produced as a 4-ml product (100mg/vial). Three sites manufactured the frozen product. Bioferon frozen product (manufactured in Germany) was used in Phase I studies, UCB-Pharma frozen product (manufactured in Belgium) was used in Phase I/II studies and Biogen frozen product (manufactured in USA) was used in Phase II/III studies.

The Sponsor reports three methods of synthesis during development of Hirulog: 1/ a solid-phase peptide synthesis method, 2/ a homogeneous-phase peptide synthesis on pilot scale and 3/ a modified homogeneous-phase peptide synthesis on commercial scale.

The Sponsor indicates that the purification step is identical procedures in 1, 2 and 3. The differences In Processes 2 and 3 are indicated to be the choice of protecting groups and the strategy of assembly of the sub-fragments. The Sponsor claims that the pilot scale lyophilized product evaluated in C93-310 and the commercial scale chemistry lyophilized product evaluated in C93-316 are identical.

In addition to the Hirulog lots tested in the NDA, three additional lots of Hirulog (Lots 41692, 41693 and 42376) were manufactured for use in clinical trials. The FDA field investigator has noted that these lots were manufactured under non-GMP conditions and were made according to a slightly different manufacturing process than that used for all the lots used in the NDA studies. Because of the difficulties in this manufacturing process, [redacted] (the manufacturing contract laboratory) has proposed a modified method for preparation of future lots. This process has not been submitted for CMC review, although a brief description was provided to Dr. A. Shaw, Chemistry Reviewer, in a meeting with the Sponsor on July 27, 1998. This procedure is expected to be used to manufacture the commercial product and all lots to be used for future trials. According to Dr. A. Shaw, the manufacturing procedure used to prepare the lots used in the NDA trials, the procedure used to prepare the three lots (Lots 41692, 41693 and 42376), and the proposed new commercial procedure (July 1998) are similar enough such that there is no reason to expect that these lots of bivalirudin drug product will not be bioequivalent as long as equivalent antithrombin activity is achieved with these products.

In response to the Agency's request, the Medicines Company has validated a chromogenic assay for assessment of antithrombin activity and has proposed a 42% to 52% spec, based on this validated assay. In the bivalirudin lots used in the NDA studies, although there are uncertainties in the manner the specs were determined, the antithrombin activity of these bivalirudin lots are claimed to be "45% to 50%".

The proposed dosage form of bivalirudin is 250 mg lyophilized powder for solution in a 10 ml [redacted] glass vial. To reconstitute, 5 ml of water for injection (USP) should be added to each vial of lyophilized Hirulog injectable product. Following dissolution of all the material in the vial, the reconstituted Hirulog injection will contain 50 mg/ml bivalirudin, sodium hydroxide, NF, 4.35 mg/ml, and mannitol, USP, 25 mg/ml The proposed new commercial formulation (July 1998) may also contain trifluoroacetic acid to adjust the pH.

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[redacted]

Pharmacodynamic measurements:

Methods/equipment used for the pharmacodynamic measurements are not described. This is particularly important for across-study assessments. The aPTT measures are indicated to be performed at the clinical sites, some of which were in the United States and some of which were in England. The global coagulation methods are reported to be highly variable and highly dependent on the systems and the reagents used for measurements (6-9). The information supporting the pharmacodynamic measurements has been requested from the Sponsor.

In response to this question, in the October 19, 1998 Amendment, the Sponsor has provided information on aPTT measurements from 5 clinical sites that participated in the Phase II Study, Study C90-041. This information is included in Appendix B.

4. An overview of submitted pharmacokinetic/pharmacodynamic studies

An overview of the submitted clinical pharmacology and biopharmaceutics studies is given in the following table, Table 2. Because of outstanding issues, data from the Hirulog studies can not be considered final and an in depth discussion or assessment of data from the individual study reports can not be provided. However, to provide a scope of the conducted studies, synopses of individual study reports provided by the Sponsor are included in Attachment C. Bioequivalence studies are also discussed in detail in this section.

Table 2: A Tabulated Overview of Hirulog Clinical Pharmacology Reports

Vol., Study Number	Study title, methods	Comments
1.039 and 1.04, C90-010	**Title**: A phase I, dose escalating study of BG8967 in normal male volunteers. **Methods:** Doses of BG8967 were administered as a 15 min iv infusion (0.05, 0.075, 0.15, 0.3 and 0.6 mg/kg), as IV bolus (0.3 mg/kg) or as a 2 h infusion at a rate of 0.6 mg/kg/h. Twelve and twenty-four hour infusions of BG8967 were at 0.3mg/kg/h dose with aspirin. Subcutaneous doses of BG8967 (0.3 mg/kg, 0.6 mg/kg and 1.0 mg/kg) were also administered. Plasma BG8967 concentration-time profiles could be characterized only for the 0.3 and 0.6 mg/kg BG8967 doses. Anticoagulant activity was measured based on activated clotting time (ACT), aPTT, PT and TT.	This study is referred to in the PI, as evidence of linear dose- and concentration-dependent anticoagulant activity of Hirulog. However, based on the activated clotting time (ACT), aPTT, PT and TT, and plasma BG8967 parameters obtained at 2 doses, it is not possible to claim linear dose- and concentration-dependent anti-coagulant activity.
1.041, C91-125	**Title:** A Phase I dose tolerability study of different formulations of BG8967 given subcutaneously to normal volunteers. **Methods:** Tolerability of 3 s.c. formulations (BG8967 in phosphate buffer, NaOH or in TRIS)in healthy male volunteers was evaluated.	Consistent with the study protocol, there is no pharmacokinetic information
1.042, C92-305	**Title:** An open label, randomized, crossover study to compare the pharmacokinetic profiles of two formulations of BG8967 in healthy volunteers. **Methods:** Frozen formulation used in clinical trials and refrigerated experimental formulation were administered at 0.5 mg/kg/h dose for 4h as iv infusion in a randomized cross-over fashion to healthy male (n=10) and female (n=10) volunteers. Blood samples were collected for BG8967 and aPTT measurements.	The Sponsor claims that the pharmacokinetic parameters are similar for the two formulations (the refrigerated formulation is not pertinent for this submission). A difference between the formulations is in the increased incidence of nausea with the refrigerated solution. A study is recommended for further assessment.

Table 2 continued: A Tabulated Overview of Hirulog Clinical Pharmacology Reports

Vol., Study Number	Study title, methods	Comments
1.043, C92-306	**Title:** A double-blind, randomized, placebo-controlled study to determine the tolerability and to compare the pharmacokinetic profiles of various formulations of BG8967 in healthy volunteers. **Methods:** The study would be conducted in 2 phases. In Phase I, frozen BG8967 formulation used in clinical trials or a placebo were to be administered at 0.5 mg/kg/h dose for 4h as iv infusion in a randomized cross-over fashion to healthy female volunteers. In Phase II, volunteers would have received one of the 5 formulations of BG8967 or placebo. Blood samples were collected for BG8967 and aPTT measurements.	One of the 2 planned phases was completed because of an adverse event observed in one of the volunteers. Limited pharmacokinetic data are provided.
1.044, C93-310	**Title:** A double-blind, randomized, placebo-controlled study to determine the tolerability and to compare the pharmacokinetic profiles of two formulations of BG8967 in healthy volunteers. **Methods:** This study, although not initially intended, is now being filed as the primary evidence of bioequivalence of the frozen and lyophilized bivalirudin formulations. BG8967 frozen formulation used in clinical trials, lyophilized BG8967 formulation or placebo (saline) was administered to each volunteer at 0.5 mg/kg/h dose for 4h as iv infusion in a randomized cross-over fashion to healthy male volunteers. Each infusion was separated by 7 days and 3 months later, lyophilized formulation of BG8967 was administered as rechallenge. Blood samples were collected to measure BG8967, aPTT and antibody formation. Assay method is described in the report but there is no information on assay validation, assay performance during sample analysis or effect of storage conditions on samples. In Sponsor's comparison of the two formulations of BG8967, period and period and treatment interactions were noted.	Following recalculation and reanalysis of pharmacokinetic parameters, the source of period and period*treatment effect seen in some of the pharmacokinetic parameters was identified. Use of an incomplete data set from one of the subjects to estimate an AUC value had resulted in this observation. In addition, errors were noted in calculation of AUC values. Reanalysis of data and recalculation of 90% confidence intervals by the reviewer, albeit remaining analytical issues, supports the Sponsor's conclusion that the Hirulog formulations (pilot scale frozen and commercial scale chemistry lyophilized) are bioequivalent. However, analytical issues need to be resolved to reach this conclusion.

Table 2 continued: A Tabulated Overview of Hirulog Clinical Pharmacology Reports

Vol., Study Number	Study title, methods	Comments
1.045 and 1.046, C93-313	**Title:** A pharmacokinetic and pharmacodynamic study of BG8967 in subjects with renal insufficiency. **Methods:** BG8967 was administered to subjects with normal renal function (n=8), mild (n=8, GFR: 60-89 ml/min/1.73m^2), moderate (n=7, GFR: 30-59 ml/min/1.73m^2) and severe renal impairment (n=10, GFR: <30 ml/min/1.73m^2). BG8967 was also infused to dialysis-dependent subjects (n=8) requiring maintenance hemodialysis at least twice per week. BG8967 doses, except two of the subjects with severe renal impairment, were infused at 0.5 mg/kg/h for 4 h and two doses (0.5 mg/kg/h and 0.25 mg/kg/h) of BG8967 were evaluated in dialysis patients. Blood samples were collected to measure BG8967 and aPTT.	Dose adjustment is suggested/recommended in patients with moderate and severe renal impairment. Also bivalirudin can be dialysed and dose-adjustment (a step-up increase in infusion rate) may be needed during dialysis.
1.047, C93-316	**Title:** A double-blind, randomized, cross-over study to determine the tolerability and to compare the pharmacokinetic profiles of BG8967 injection prepared using homogeneous-phase pilot chemistry versus homogeneous-phase commercial chemistry **Methods:** Hirulog formulations (pilot chemistry, frozen and commercial chemistry, lyophilized) were evaluated in healthy male volunteers. BG8967 formulations were administered to each volunteer at 0.5 mg/kg/h dose for 4h as iv infusion in a randomized cross-over fashion. Each infusion was separated by 7 days. Blood samples were collected to measure BG8967 and aPTT. Urine samples were also collected. However, BG8967 is reported to be unstable in urine under the conditions it was collected in this study.	Bivalirudin in samples could not be assayed. The sample integrity is indicated to be compromised due to lack of temperature control (mechanical difficulties with the air-conditioning unit). Based on aPTT, E_{max} and E_{AUC} values, both formulations are claimed equivalent. However, as discussed under bioequivalence studies, there is also additional information demonstrating that these parameters are not as discriminatory as bivalirudin plasma concentrations and can not be used for bioequvalence assessment.

Table 2 continued: A Tabulated Overview of Hirulog Clinical Pharmacology Reports

Vol., Study Number	Study title, methods	Comments
1.048, C93-317	**Title:** An open label, randomized, cross-over study in healthy volunteers to evaluate the interaction of BG8967 and heparin. **Methods:** Subjects (n=6) randomly assigned to two dosing sequences, received both treatments: heparin followed by BG8967 or BG8967 followed by heparin. Treatment periods were separated by 7 days. Blood samples were collected to measure BG8967, heparin and aPTT.	A 30 min. interval between discontinuation of bivalirudin and initiation of heparin is recommended.
1.065, C94-321	**Title:** The antihemostatic effects of BG8967 in subjects with renal failure treated with chronic hemodialysis **Methods:** aPTT measurements were made after iv bolus, iv infusion and sc doses of BG8967. Different dosing regimens, based on aPTT were evaluated.	Bivalirudin was well-tolerated and results in a predictable effect in patients on dialysis.
1.066, 1.067. 1.068, 1.069 and 1.070, C90-041	**Title:** A dose ranging study of BG8967 in routine percutaneous transluminal coronary angioplasty (PTCA) **Methods:** Six dosing regimens were evaluated in patients. BG8967 iv bolus doses 0.15, 0.25, 0.35, 0.45, 0.55 or 1 mg/kg were followed by 4 h infusion of 0.6, 1.0, 1.4, 1.8, 2.2 and 2.5 mg/kg/h doses of BG8967, respectively. If the site of the lesion was unstable, infusion of BG8967 continued at 0.2mg/kg/h. Coagulation parameters were measured in all patients and BG8967 were measured in some patients.	If analytical issues can be resolved, pharmacokinetic data from this patient population would be useful. Furthermore, this is the only study where pharmacokinetic information may be available at the recommended clinical dose.

Bioequivalence:

The specificity of the assay utilized for bivalirudin quantitation is uncertain. As a result, the following summary of studies and their results are presented for information purposes and not as an indication of their acceptability for assessment of bioequivalence of the commercial scale lyophilized formulation (proposed market formulation) to the pilot frozen formulation used in the efficacy trials. An additional assumption that is also questioned by the reviewer is the one to one correlation of plasma "bivalirudin" measurements and antithrombin activity of the Hirulog formulations.

In June 1993, Biogen as the Sponsor, had outlined a series of studies to evaluate bioequivalence of the commercial scale lyophilized formulation to the pilot scale frozen formulation used in the efficacy trials. However, in October 1994, Biogen proposed to submit results from two studies, C93-310 (as pivotal) and C93-316 (as supportive) evidence of bioequivalence of the lyophilized commercial scale synthesis

formulation to the pilot scale frozen formulation of Hirulog.

Study C93-310:

The objective of Study C93-310 was to determine tolerability and pharmacokinetic profiles of two formulations of bivalirudin following administration of 0.5 mg/kg/h Hirulog as a 4 h infusion to 15 healthy male volunteers. The formulations tested were pilot scale frozen formulation (Lot 67Z01S), pilot scale lyophilized formulation (Lot 67Z04S) and placebo. Frozen and lyophilized Hirulog formulations and placebo were administered according to a three-way randomized double-blind cross-over design on three occasions separated by a week. Three months later, lyophilized Hirulog formulation was administered to all volunteers as rechallenge to test for its antigenic effects.

The original planned analysis was a comparison of bivalirudin pharmacokinetic parameters and activated partial thromboplastin time (aPTT) E_{max} and E_{AUC} values. Statistical comparison of bivalirudin pharmacokinetic parameters (Cmax, and AUC(0-28)), E_{max} and E_{AUC} of aPTT measurements obtained from the frozen and the lyophilized formulation was performed by ANOVA testing for treatment, period and subject effects. Although not detailed in the text of the report, in the appendices, a statistically significant treatment effect was observed for AUC(0-28) and significant treatment and period effects were observed for E_{max} and E_{AUC}. Statistical comparison of the lyophilized formulation administered on two occasions was also performed by ANOVA GLM procedure testing for treatment and subject effects and a statistically significant difference was observed in E_{max} values. In general, bivalirudin values (Cmax and AUC(0-28)) were higher for the lyophilized formulation than the frozen formulation. The mean Cmax values after the frozen formulation, lyophilized formulation and the rechallenge lyophilized formulation were 1474 ng/ml, 1668 ng/ml, and 1935 ng/ml, respectively with corresponding AUC(0-28) values of 5638 ng.h/ml, 6202 ng.h/ml and 7369 ng.h/ml.

Study C93-316:

The Study C93-316 was originally intended as the pivotal bioequivalence study for comparison of the two formulations of Hirulog, pilot scale frozen formulation (Lot 67A04Z) and commercial scale synthesis lyophilized formulation (Lot 67A02Q). Hirulog doses of 0.5 mg/kg/h were administered as a 4h infusion to 18 healthy male volunteers according to a two-way randomized cross-over design one week apart. Bivalirudin concentrations were identified as a measure of assessment of bioequivalence. However, the Sponsor claims that sample integrity was compromised because of lack of temperature control (due to mecnanical difficulties with air-conditioning) and bivalirudin concentrations in samples could not be measured. As a resuit, only the pharmacodynamic parameter, activated partial thromboplastin time (aPTT) was measured in this study.

Reanalysis of data from C93-310:

After completion, Study C93-316 was considered to be a supportive study for the bioequivalence claim and the report for Study C93-310 was amended to reflect the reanalysis of data in order to support the bioequivalence of the lyophilized formulation (commercial scale synthesis) to the frozen formulation (pilot scale).

Bivalirudin pharmacokinetic parameters and aPTT effect measures from Study C93-310, excluding the data from the rechallenge phase, were analyzed by ANOVA. Except for significant period and period and treatment interaction effects, there were no other statistically significant differences. The two one-sided

t-test approach was utilized to calculate 90% confidence intervals of log-transformed bivalirudin pharmacokinetic parameters (AUC(0-28), AUC(0-infinity) and Cmax) and aPTT efficacy parameters (E_{max} and E_{AUC}). All of these parameters yielded 90% confidence intervals that were within the 80% to 125% range. The period and period and treatment interaction effects were noted in the study report but not mentioned in Section 6 of the NDA.

Analytical information (such as assay performance before and during sample analysis) was not provided in the NDA and it is not possible to determine whether the period effect and/or the treatment-period interaction may be assay related. However, a closer review of the data from C93-310 showed that the observed period and treatment interaction could be attributed to inclusion of an incomplete data set and hence, incorrect AUC calculation from one of the subjects. The statistical analysis of data, including calculation of 90% confidence intervals for "bivalirudin" Cmax and AUC values by the reviewer confirms the Sponsor's conclusion that the confidence intervals were within the 80% to 125% range. The concerns regarding the nonspecificity of the bivalirudin assay and its impact on assessment of data from Study C93-310 have been communicated to the Sponsor. In the most recent amendment, the Sponsor has indicated that they will be continuing to work on the assay related issues.

Proposed use of aPTT data to link Studies C93-310 and C93-316:

In Study C93-316, log-transformed aPTT parameters (E_{max} and E_{AUC}) were analyzed by ANOVA. There were no statistically significant treatment, sequence, and period effects. However, a significant subject within sequence effect was noted for both parameters. The 90% confidence intervals calculated for the aPTT parameters by the Sponsor are within the 80% to 125% range and based on this data, the Sponsor claims that the two Hirulog formulations (frozen pilot scale synthesis and lyophilized commercial scale synthesis) tested in this study were bioequivalent.

In addition, the Sponsor also claims that based on superimposability of aPTT mean profiles and plasma bivalirudin concentrations obtained in Study C93-310, and the similarity of mean aPTT profiles from Studies C93-316 and C93-310, the data from the two studies can be linked, and Study C93-316 can be used to support C93-310. The aPTT results obtained from the two studies are illustrated in the following figures, Figures 1 and 2.

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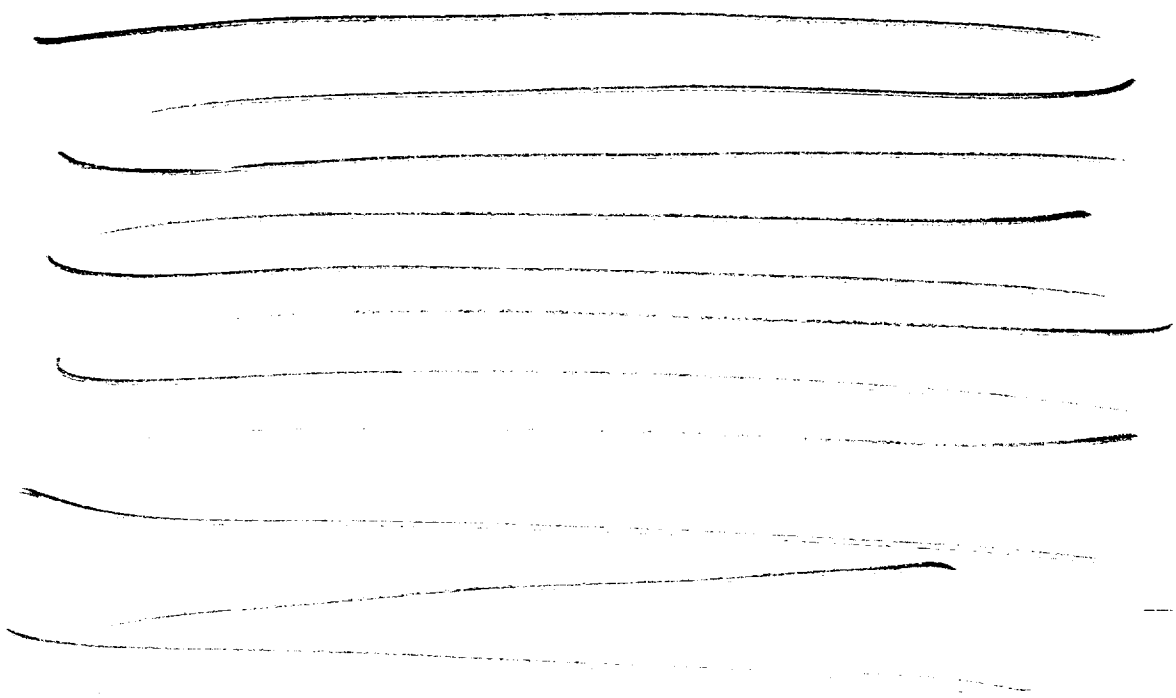
Figure 2: Mean aPTT measurements obtained after pilot scale frozen formulation and commercial scale synthesis lyophilized formulation (C93-316)



The average aPTT values as a function of time appear comparable across the two studies, however, it is important to note that while similar aPTT mean Emax values were obtained in both studies, bivalirudin mean Cmax values were slightly different for the two Hirulog formulations. In Study C93-310, bivalirudin mean Cmax values were 1474 ng/ml, 1668 ng/ml and 1935 ng/ml, following administration of the frozen formulation, lyophilized formulation and the second administration of the lyophilized formulation, respectively. The corresponding aPTT mean E_{max} values were 52.3, 51.6 and 53.9 sec. In Study 93-316, aPTT mean E_{max} values were 58.5 and 59.5 sec for the frozen and the lyophilized formulations.

Furthermore, as illustrated in Figure 3, aPTT is not a discriminatory parameter suitable for bioequivalance assessment.

Figure 3: Maximum BG8967 concentrations and steady-state aPTT measurements (C90-041)

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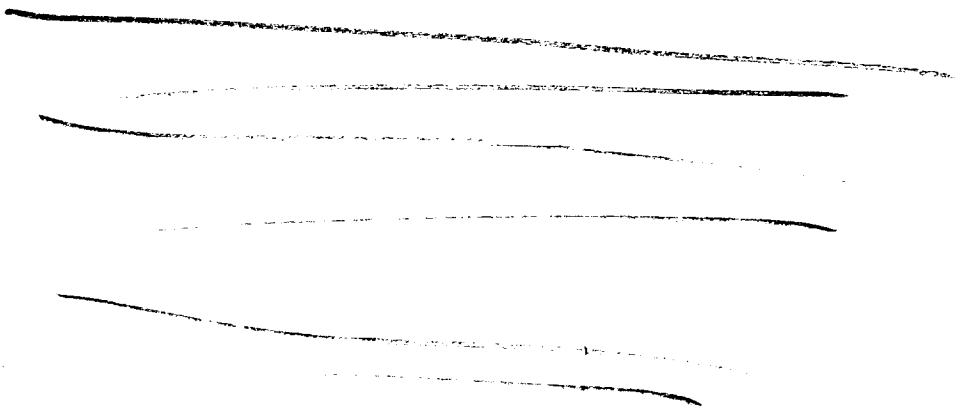

Similar aPTT E_{max} values are obtained for Hirulog doses of 0.6 mg/kg/h and 1 mg/kg/h while plasma bivalirudin mean Cmax value for the 1 mg/kg/h dose was approximately twice the value for the 0.6 mg/kg/h dose.

Even with the uncertainties related to the specificity of the ELISA assay, these results strongly support that bivalirudin concentrations are needed for accurate comparison of Hirulog formulations and that aPTT measurements are not suitable to link the data from C93-310 and C93-316. Significant differences in aPTT measurements are reported due to differences in commercially available aPTT reagents (6-9).

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5. References

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ATTACHMENT C: Synopses of the Hirulog PK and PD studies.

STUDY SYNOPSIS
Study Number C90-010

A Phase I, Dose-escalating Study of BG8967
in Normal Male Volunteers

INVESTIGATOR

- Dr. TGK Mant, Guy's Drug Research, Ltd., London, United Kingdom

OBJECTIVE

- Primary: Test the safety of BG8967 when administered intravenously (IV) or subcutaneously (SC), alone or in combination with aspirin (ASA), to normal male volunteers.
- Secondary: Determine the tolerability of BG8967 when administered IV or SC to normal male volunteers. Determine the pharmacokinetics of IV or SC BG8967 administration, alone or in combination with ASA, to normal male volunteers. Determine the pharmacodynamic effects of various doses of BG8967, alone or in combination with ASA, by monitoring coagulation parameters (bleeding time, activated partial thromboplastin time, prothrombin time, thrombin time, platelet aggregation). Identify potential BG8967 dose levels to be used in Phase II studies.

STUDY DESIGN

- Single-blind, placebo-controlled, dose escalation study in healthy males.
- Blood drawn for measurement of coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT).
- Blood drawn for measurement of fibrinogen levels and collagen-induced and ADP-induced platelet aggregation assays.
- Blood drawn for plasma levels of BG8967.
- Blood drawn for determination of BG8967 antibody formation.
- Urine collected for measurement of total urine volume, urine creatinine levels, and excretion levels of BG8967.
- Safety monitored by vital signs, ECG monitoring, physical examination, assessment of bleeding including bleeding time, blood chemistry, hematology, coagulation parameters, urinalysis, measurement of fecal occult blood, and adverse event reporting.

TEST DRUG SCHEDULE

- BG8967 administered via IV infusion over 15 minutes, 2 hours, 12 hours, or 24 hours, or via IV bolus, or via two SC injections to the abdomen. A 48 hour IV infusion was planned but not done.
- Doses used for 15 minute IV infusions were 0.05 mg/kg, 0.075 mg/kg, 0.15 mg/kg, 0.3 mg/kg and 0.6 mg/kg.
- Doses used for SC administration were 0.3 mg/kg, 0.6 mg/kg, and 1.0 mg/kg.
- Dose used for IV bolus was 0.3 mg/kg.
- Dose used for 2 hour IV infusion crossover with placebo or aspirin was 0.6 mg/kg/h.
- Dose used for 12 and 24 hour IV infusions with aspirin was 0.3 mg/kg/h.

POPULATION

- Seventy-two healthy male volunteers.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, defects in platelet function and coagulation factor activity, history of cardiovascular and/or peripheral vascular disease, predisposition to development of keloid formation, history of severe allergic or anaphylactic or transfusion reactions.

RESULTS

- A total of 72 male subjects, 18 to 36 years of age, were recruited. Fifty four received BG8967 and 18 received placebo. All subjects completed the study.
- Mean area under the curve (AUC), peak concentration (C_{max}), time of peak concentration (t_{max}), half-life, clearance, and area under the aPTT-, PT- and TT-time curves adjusted from pre-dose appear on the next page.
- Concurrent administration of aspirin does not influence the pharmacokinetic or anti-thrombotic properties of BG8967.
- Plasma AUC was linearly related to dose of BG8967.
- Kinetic evaluation demonstrated that antithrombotic effects of BG8967 were linearly related to plasma BG8967 AUC.
- Mean renal excretion as a percentage of total elimination ranged from 9.9% to 21.8% across all dose groups.
- The most commonly reported adverse events were headache (11% on BG8967 and 11% on placebo), injection site pain (13% on BG8967 and 6% on placebo), postural

hypotension (7% on BG8967 and 22% on placebo), injection site hemorrhage (7% on BG8967 and 6% on placebo).

- The bleeding time was within the normal range for the majority of subjects.

Placebo-Controlled Dose-Escalation

Route	Dose (mg/kg)	Number of Subjects	AUC† (min.μg/mL)	C_{max} (ng/mL)	t_{max} (min)	Half-life (min)	Clearance (mL/min)	Vd (L)	aPTT$_{max}$ (min.s)	PT$_{max}$ (min.s)	TT$_{max}$ (min.s)
15 min	Placebo	10	-	-	-	-	-	-	-58	68	-353
IV	0.05	4	-	69	15.0	-	-	-	985	251*	1148*
infusion	0.075	4	-	234	15.7	-	-	-	1442*	152	2123*
	0.15	4	-	679	15.0	-	-	-	1255*	214	2220*
	0.3	4	46.56	1271	15.5	22.5	545	16.67	1081	273*	1960*
	0.6	4	96.10	4309	15.5	24.6	472	16.82	1860*	628*	4144*
SC	Placebo	6	-	-	-	-	-	-	-668	54	-347
injection	0.3	4	-	0	-	-	-	-	2836*	773*	5030*
	0.6	4	-	377	-	-	-	-	4414*	955*	11318*
	1.0	4	-	528	-	-	-	-	5625*	1318*	12659*
IV bolus	Placebo	2	-	-	-	-	-	-	-374	27	113
	0.3	4	28.53	1975	2.0	12.2	865	13.65	2432*	251*	2868*

* Means are statistically significant different from placebo, $p < 0.05$.
† AUC based on fitted pharmacokinetic models.

Crossover with Placebo or Aspirin

Eight subjects received 0.6 mg/kg/h for 2 h co-administered with	AUC† (min.μg/mL)	C_{max} (ng/mL)	t_{max} (h)	Half-life (min)	Clearance (mL/min)	Vd (L)	aPTT$_{max}$ (min.s)	PT$_{max}$ (min.s)	TT$_{max}$ (min.s)
Placebo	275	2647	1.56	23.3	334	10.98	9118	1349	8349
Aspirin	310	2918	1.72	23.8	286	9.84	9015	1429	8481

† AUC based on fitted pharmacokinetic models.

Prolonged Infusion

Five subjects in each group received aspirin with 0.3 mg/kg/h IV infusion for	AUC† (min.μg/mL)	C_{max} (ng/mL)	t_{max} (h)	Half-life (min)	Clearance (mL/min)	Vd (L)	aPTT$_{max}$ (min.s)	PT$_{max}$ (min.s)	TT$_{max}$ (min.s)
12 h	841	1116	7.40	28.6	365	14.66	29544	3615	32391
24 h	1752	1125	24.0	31.4	300	12.95	56645	7619	66658

† AUC based on fitted pharmacokinetic models.

CONCLUSIONS

- BG8967, a direct thrombin inhibitor, was found to be an active anticoagulant without significant bleeding time prolongation in a study with human volunteers.
- Single dose studies demonstrated that the drug was well-tolerated.
- Dose-dependent prolongations in clotting time variables were observed, with excellent correlation of these changes to the pharmacokinetics for the peptide.
- The short half-life of BG8967 leads to rapid reversal of its anticoagulant activity.
- The renal excretion of BG8967 comprises approximately 10 to 20% of the administered dose suggesting that renal excretion of BG8967 accounts for only a small component of the clearance.

- Prolonged infusion of BG8967 in subjects receiving aspirin was well-tolerated and showed no apparent interactions of the two drugs. There was a stable and consistent prolongation of the aPTT at the doses used without evidence for a cumulative effect.
- The pharmacokinetic profile of intravenous BG8967 was not importantly influenced by dose, duration of infusion, or co-administration of aspirin.
- The tolerability and pharmacodynamic properties of BG8967 support continued evaluation of this therapeutic agent in the management of arterial and venous thrombosis.

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STUDY SYNOPSIS
Study Number C90-041

A Dose-Ranging Study of BG8967 in Routine
Percutaneous Transluminal Coronary Angioplasty (PTCA)

Change	*Protocol Version*	*Date*
Administrative Change 1[1]	2	November 8, 1990
New Protocol Version (Appendix I.A)	2	December 18, 1990
Amendment 2 (Appendix I.B)	3	February 25, 1991
Administrative Change 2 (Appendix I.C)	4	April 8, 1991
Amendment 3 (Appendix I.D)	5	May 9, 1991
Amendment 4 (Appendix I.E)	6	August 1, 1991
Amendment 7	NA	September 13, 1991
Amendment 8	NA	January 27, 1992
Amendment 9 (Appendix I.F)	7	November 3, 1992

[1]Incorporated directly into Version 2 of the protocol.
Note: There is no Amendment 1 per Version 3.
Note: There are no Amendments 5 and 6 to this protocol (Biogen memo dated January 21, 1994).

INVESTIGATORS

- Dr. R. Bonan, Montreal Heart Institute, Montreal, Canada
  Dr. D. de Bono, Glenfield General Hospital, Leicester, U.K.
  Dr. M.D. Cohen, Indiana Heart Physicians, Beech Grove, IN.
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  Dr. U. Sigwart, Royal Brompton National Heart and Lung Hospital, London, U.K.
  Dr. J. Strony, University Hospitals of Cleveland, Cleveland, OH.
  Dr. E.J. Topol, University of Michigan, Ann Arbor, MI. and Cleveland Clinic Foundation, Cleveland, OH.
  Dr. J.T. Willerson, University of Texas Medical School, Houston, TX.

OBJECTIVES

- To determine whether BG8967 could safely replace heparin during PTCA.
- To document the frequency of abrupt vessel closure in patients administered BG8967 in routine PTCA.
- To evaluate the anti-thrombin activity of BG8967 using biochemical markers for blood coagulation.
- To determine the minimum dose for angioplasty necessary to maintain tolerability and a positive clinical effect.

STUDY DESIGN

- Open-label, multicenter, dose-ranging, Phase II.
- Antithrombin activity evaluated for dose-ranging using biochemical markers (ACT).
- Frequency of abrupt vessel closure (AVC) and complications of AVC were measured.

TEST DRUG SCHEDULE

- Each dose regimen had three stages of administration: an IV bolus pre-PTCA dilation, an infusion of 4 hours during PTCA, and, if the site of the lesion was unstable, an IV infusion of 0.2 mg/kg/h.
- Six dose regimens of BG8967:

Group	*IV bolus (mg/kg)*	*IV infusion for 4 hours (mg/kg/h)*
1	0.15	0.6
2	0.25	1.0
3	0.35	1.4
4	0.45	1.8
5	0.55	2.2
6	1.00	2.5

- In Groups 1 to 5, 0.2 mg/kg/h as an IV infusion could be administered for up to 20 hours (Hours 4-24) if the lesion was unstable. In Group 6, 0.2 mg/kg/h IV infusion was to be given to all patients for 8 hours post-PTCA.

POPULATION

- Males and females, who qualified for PTCA by virtue of >70% stenosis of the vessel intended for angioplasty.
- Major exclusion criteria: active or prior history of bleeding tendencies, disease with a potential for bleeding, stroke, or allergy to radiopaque dye.

RESULTS

- 303 patients were recruited of whom 291 were dosed with BG8967. One patient who enrolled in Group 1 was discontinued due to an adverse event.
- Of the 291 patients dosed, 240 (82%) were male and 51 (18%) were female. Ages ranged from 29 to 78 years.
- Two patients in the 1.0 mg/kg/h group died; one during hospitalization and one during follow-up.

Pharmacodynamics/Pharmacokinetics

- Plasma drug levels were dose-related and blood coagulation parameters (ACT, aPTT, PT) correlated with plasma drug concentrations.
- Hirulog demonstrated dose-dependent anticoagulation. With increasing dose, the percentage of patients achieving maximum ACT levels >300 seconds increased. For the lowest dose, this percentage was 12% while for the highest dose this percentage was 100%.

Efficacy

- These results exhibited a significant decrease in the occurrence of unsuccessful angioplasty in patients receiving the 3 higher dosing regimens, relative to patients receiving the 3 lower dosing regimens (p-value = 0.038). In addition, no patient treated at the highest dosing regimen (1.00 mg/kg bolus and 2.5 mg/kg/h IV infusion for 4 hours) reported unsuccessful angioplasty during this trial.
- Incidence of unsuccessful angioplasty defined by abrupt vessel closure and clinical events were:

Bolus (mg/kg) *Infusion (mg/kg/h)*	*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
Patients (%) achieving ACT >300 sec	12%	26%	50%	72%	84%	100%
No. of patients dosed	57	50	45	73	54	12
No. of patients evaluated	52	44	41	70	51	12
No. with unsuccessful angioplasty	3 (6%)	5 (11%)	6 (15%)	3 (4%)	2 (4%)	0 (0%)
P-values:						
1,2,3 versus 4,5,6	0.038					
1,2,3 versus 4,5	0.062					

Safety

- BG8967 was well-tolerated in doses up to a bolus dose of 1.0 mg/kg BG8967 followed by 2.5 mg/kg/h 4-hour IV infusion followed by 0.2 mg/kg/h IV infusion for up to 20 hours. One patient prematurely discontinued therapy with BG8967 due to experiencing an adverse event (transient ischemic attack). None of the patients who experienced bleeding or peripheral vascular complications died or had premature study drug discontinuation.
- Two patients, both in the BG8967 1.0 mg/kg/h group, died: etiologies were ventricular fibrillation (Patient 0525) and coronary artery disease (Patient 0704). The investigator did not consider the deaths to be related to BG8967 therapy.
- Adverse events with an incidence of 5% or greater were angina pectoris (103 patients - 35%), intravascular puncture site hemorrhage (83 patients - 29%), back pain (50 patients - 17%), ecchymosis (33 patients - 11%), nausea (23 patients - 8%), headache (22 patients - 8%), injection site pain (17 patients - 6%), bradycardia (17 patients - 6%), fever (16 patients - 5%), hematuria (15 patients - 5%), and pain (15 patients - 5%). Intravascular puncture site hemorrhage was the most common event judged to be related to the test medication (72 patients - 25%).
- The most common bleeding events were intravascular puncture site hemorrhage (83 patients - 29%), ecchymosis (33 patients - 11%) and hematuria (15 patients - 5%).

CONCLUSIONS

These individual study conclusions are supported in this report:

- BG8967 can safely be used as the primary anticoagulant in patients undergoing PTCA.
- Higher dosing regimens of BG8967 at or above 1.8 mg/kg/h are associated with a lower rate of abrupt vessel closure than lower BG8967 dosing regimens.
- Dose-related anticoagulation was observed, in particular for ACT, without an increase in bleeding or adverse events.
- Rapid achievement of steady-state ACT and plasma concentration levels was dose-dependent.

Due to dose-dependent anticoagulation effects, dose-dependent rapid achievement of steady-state ACT and plasma concentrations, a positive clinical effect in reducing AVC rates, and a maintained good safety profile,

the dosing regimen of 1.0 mg/kg IV bolus followed by a 4-hour 2.5 mg/kg/h IV infusion is considered appropriate for further investigation in Phase III trials.

STUDY SYNOPSIS
Study Number: C91-125

A Phase I Dose Tolerability Study of Different Formulations of BG8967 Given Subcutaneously in Normal Volunteers

INVESTIGATOR	• Dr T G K Mant, Guy's Drug Research Unit Limited, London, U.K.
OBJECTIVES	• To evaluate the local tolerance of BG8967 in three formulations administered by subcutaneous injection. • To determine the local tolerance of varying concentrations of new BG8967 formulations administered by a subcutaneous injection. • To identify a well-tolerated formulation of BG8967 that will allow a smaller dose volume to be administered subcutaneously.
STUDY DESIGN	• Double-blind, placebo-controlled, Phase I study in two parts. • Part I was a randomized block design in which each of 8 subjects received three formulations of BG8967 and one saline control as 0.5 mL subcutaneous injections in random order into four different sites in the anterior abdominal wall. • Part II was a combined randomized block and crossover design in which 8 subjects received two different concentrations of each of the two new formulations as 0.5 mL subcutaneous injections, in random order, into two of four different sites; they received one formulation on one occasion, the other on a separate occasion.
TEST DRUG SCHEDULE	• Part I: 0.5 mL subcutaneous injections of BG8967 (25 mg/mL) in phosphate buffer (frozen formulation), sodium hydroxide (NaOH) or tromethamine (TRIS) (both new formulations) and saline control. • Part II: 0.5 mL subcutaneous injections of BG8967 at 25 mg/mL and 75 mg/mL in either NaOH or tromethamine (TRIS).
POPULATION	• 16 healthy male subjects, 8 subjects in each part. • Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.
RESULTS	• 16 males, aged 21 to 29, completed the study. No one withdrew. • All subjects were included in analysis of local tolerability and safety. Subcutaneous injections caused only minimal and very transient local pain. Minor bruising occurred at the site of the injection. • In Part I of the study, subjects considered injections of BG8967 in phosphate buffer to be slightly more painful than the other treatments immediately post-dosing. • In Part II of the study BG8967 (75 mg/mL) in tromethamine emerged as the least painful formulation. • No significant difference was observed in terms of local erythema and swelling between any of the formulations used in either Parts I or II of the study. • Physical examination, urinalysis, plasma biochemistry, hematology and electrocardiography showed no evidence of clinically significant toxicity of BG8967.
CONCLUSION	• BG8967 in tromethamine and BG8967 in sodium hydroxide at concentrations of 75 mg/mL were well tolerated and are suitable for further study in Phase II/III clinical trials.

STUDY SYNOPSIS
Study Number C92-305

An Open Label, Randomized, Crossover Study to Compare the Pharmacokinetic Profiles of Two Formulations of BG8967 in Healthy Volunteers

INVESTIGATOR

- Dr. T.G.K. Mant, Guy's Drug Research Unit, Ltd., London, U.K.

OBJECTIVES

- To estimate the pharmacokinetic profiles of two formulations of BG8967 (referred to as BG8967F and BG8967R) during and following a 4 hour infusion at 0.5 mg/kg/h.
- To correlate plasma drug levels with activated partial thromboplastin times (aPTT).

STUDY DESIGN

- Open label, randomized, crossover in healthy volunteers.
- Subjects randomized into one of two treatment sequences.
- Blood drawn during infusion and the 24 hour period after infusion for determination of plasma concentrations of BG8967 and aPTT.
- Urine collected during infusion and the 24 hour period after infusion for determination of concentrations of BG8967 in urine.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.

TEST DRUG SCHEDULE

- Two formulations of BG8967, one frozen (BG8967F) used in clinical trials and one experimental refrigerated solution formulation (BG8967R).
- Day 1: Each subject received one 4 hour infusion of the randomly selected test formulation at the rate of 0.5 mg/kg/h.
- Day 8: Each subject received one 4 hour infusion of the alternate test formulation at the rate of 0.5 mg/kg/h.

POPULATION

- Healthy male and healthy female subjects.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS

- 11 subjects randomized to BG8967F then BG8967R, 9 subjects randomized to BG8967R then BG8967F.
- 10 males and 10 females, aged between 20 and 31, completed the study. However, one male had infusion of BG8967R discontinued 5 min earlier than scheduled due to sweating, nausea and vomiting.
- Least squares mean area under the curve from 0 to 28 hours (AUC_{0-28}) and from 0 to infinity ($AUC_{0-\infty}$), peak concentration (C_{max}), time of peak concentration (t_{max}), terminal slope (λ_z), half-life, clearance, and volume at steady state (V_{ss}) from crossover analyses of variance were

	AUC 0-28 (h.ng/mL)	AUC 0-∞ (h.ng/mL)	C_{max} (ng)	t_{max} (h)	λ_z (h^{-1})	Half-life (h)	Clearance (mL/min/kg)	Vss (L/kg)
BG8967F	7608.9	7627.6	2065.9	3.77	1.14	1.51	4.52	0.18
BG8967R	7483.0	7851.2	1959.6	3.07	0.94	1.20	4.65	0.17

- The formulations were bioequivalent with respect to AUC_{0-28} and C_{max}. BG8967F had significantly longer t_{max} than BG8967R ($p=0.016$).
- A significant relationship between aPTT and plasma concentrations was evident in each subject during and following each formulation.
- The most common treatment emergent signs and symptoms following BG8967F were dizziness (25%), syncope (10%), nausea (10%) and sweating (10%). For BG8967R, the most common events were nausea (60%), vomiting (30%), dizziness (30%), sweating (20%) and injection site pain (15%).

CONCLUSIONS

- Pharmacokinetic parameters for BG8967F and BG8967R were similar, while small differences were observed in t_{max}.
- Both BG8967F and BG8967R showed anticoagulant activity in normal volunteers. Pharmacodynamics of the two formulations were similar.

- A significant increase in the incidence of nausea and vomiting was observed for BG8967R, indicating that this formulation was not well tolerated.
- Further study of the tolerability of BG8967R is warranted.

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STUDY SYNOPSIS
Study Number C92-306

A Double-Blind, Randomized, Placebo-Controlled Study to Determine the Tolerability and to Compare the Pharmacokinetic Profiles of Various Formulations of BG8967 in Healthy Volunteers

INVESTIGATOR

- Dr. S. Oliver, G. H. Besselaar Associates, Leeds, U.K.

OBJECTIVES

- To determine the tolerability to, and to estimate the pharmacokinetic profiles during and following 4 hour infusions of 0.5 mg/kg/h of various formulations of BG8967.
- To correlate plasma drug levels with activated partial thromboplastin time (aPTT).

STUDY DESIGN

- Study to be conducted in two phases in healthy volunteers.
- Phase I (double-blind, randomized crossover): ten female subjects to be randomized to one of two treatment sequences: BG8967R (a refrigerated formulation used in study C92-305) then placebo, or placebo then BG8967R.
- Phase II (double-blind, randomized, parallel group): thirty female subjects to be randomized to one of five different formulations of BG8967 or placebo. If tolerated, an additional ten males would be dosed.
- Blood drawn during infusion and the 24 hour period after infusion for determination of plasma concentrations of BG8967 and aPTT.
- Urine collected during infusion and the 24 hour period after infusion for determination of concentrations of BG8967 in urine.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.

TEST DRUG SCHEDULE

- Phase I: On Day 1, each subject to receive one 4 hour infusion of either placebo or BG8967R at the rate of 0.5 mg/kg/h; on Day 8, each subject to receive the alternate treatment during a four hour infusion. If the formulation was not well-tolerated, Phase II was to be initiated.
- Phase II: Each subject to receive one 4 hour infusion of a formulation of BG8967 at the rate of 0.5 mg/kg/h, or placebo.

POPULATION

- Healthy male and healthy female subjects.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS

- 8 female subjects, aged between 20 and 35, were recruited to Phase I, of whom 4 were randomized to placebo then BG8967R, and 4 to BG8967R then placebo.
- One subject was withdrawn prior to the second dosing period due to low hemoglobin from multiple venipuncture.
- One subject with pre-existing arteriovenous malformation had an intra-cranial hemorrhage 18 days following dosing with BG8967R (i.e., off-study). Therefore, Phase I of the study was terminated early, and phase II was not initiated.
- Mean area under the curve from 0 to 28 hours (AUC_{0-28}) and from 0 to infinity ($AUC_{0-\infty}$), peak concentration (C_{max}), time of peak concentration (t_{max}), terminal slope (λ_z), half-life, clearance, and volume at steady state (V_{ss}) were

AUC 0-28 (h·ng/mL)	AUC 0-∞ (h·ng/mL)	C_{max} (ng/mL)	t_{max} (h)	λ_z (h^{-1})	Half-life (h)	Clearance (mL/min/kg)	Vdss (L/kg)
5475.7	5073.9	1464.5	3.5	1.11	0.70	6.32	0.23

- Mean aPTT at the various time points:

Time (h):	0	0.25	0.5	1	2	4	4.25	4.5	4.75	5	6
aPTT (s):	28.6	45.3	52.9	57.8	68.9	66.1	48.8	39.9	40.0	34.8	28.9

- For each subject, regression showed a strong positive relationship ($P < 0.05$) between aPTT and plasma concentration.

- All subjects had adverse events at some time during the study. The most common events in the placebo period were headache (57%), nausea (43%), dizziness (43%). The most common events in the BG8967R period were nausea (50%), vomiting (38%), dizziness (38%), asthenia (25%) and pharyngitis (25%).

CONCLUSIONS

- Regarding tolerability, results are inconclusive.
- Dosing with BG8967 resulted in near attainment of steady state levels.
- Consistent prolongation of aPTT in association with drug administration. aPTT directly correlated with BG8967 plasma concentration.

STUDY SYNOPSIS
Study Number C93-310

A Double-Blind, Randomized, Placebo-Controlled Study to Determine the Tolerability and to Compare the Pharmacokinetic Profiles of Two Formulations of BG8967 in Healthy Volunteers

INVESTIGATOR

- Dr. T.G.K. Mant, Guy's Drug Research Unit, Ltd., London, U.K.

OBJECTIVES

- To determine the tolerability to two formulations, frozen and lyophilized, of BG8967.
- To estimate the pharmacokinetic profiles of two formulations of BG8967 during and following a 4 hour infusion at 0.5 mg/kg/h.
- To correlate plasma drug levels with activated partial thromboplastin time (aPTT).
- To evaluate antibody formation to BG8967, particularly following repeat exposure.

STUDY DESIGN

- Double-blind, randomized, three-period, three-treatment crossover in healthy male volunteers.
- Subjects randomized into one of six treatment sequences.
- Blood drawn during infusion and the 24 hour period after infusion for determination of plasma concentrations of BG8967 and aPTT.
- Urine collected during infusion and the 24 hour period after infusion for determination of concentrations of BG8967 in urine.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.
- Subjects returned at 3 months for a 4 hour infusion at 0.5 mg/kg/h of lyophilized formulation BG8967. Blood drawn for determination of plasma concentrations of BG8967, aPTT and antibody formation.

TEST DRUG SCHEDULE

- Placebo and two formulations of BG8967: one frozen, one lyophilized.
- Each subject received each formulation once and placebo in a random order, with each infusion separated by 7 days. The lyophilized formulation was administered again, three months later.
- Each formulation of BG8967 infused for 4 hours at a rate of 0.5 mg/kg/h.
- Placebo (saline) infused for 4 hours using the same rate as for both formulations of BG8967.

POPULATION

- Healthy male subjects.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS

- In the crossover phase, 15 males, aged between 22 and 35, were enrolled into the study. One subject was withdrawn due to thrombophlebitis in the second dosing period (with placebo).
- Of the 15 subjects participating in the crossover phase, 13 returned for rechallenge with the lyophilized formulation. The remaining two subjects were unable to attend.
- Mean area under the curve from 0 to 28 hours (AUC_{0-28}) and from 0 to infinity ($AUC_{0-\infty}$), peak concentration (C_{max}), time of peak concentration (t_{max}), terminal slope (λ_z), half-life, clearance, and volume at steady state (Vdss) were

	AUC_{0-28} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	C_{max} (ng/mL)	t_{max} (h)	λ_z (h^{-1})	Half-life (h)	Clearance (mL/min/kg)	Vdss (L/kg)
Frozen	5638.44	5915.52	1474.13	3.36	1.20	0.61	6.52	0.22
Lyophilized	6202.46	6543.19	1667.54	3.14	1.25	0.61	6.24	0.21
Lyophilized (Rechallenge)	7368.56	7368.56	1935.08	3.83	1.26	0.62	4.63	0.20

- The frozen and lyophilized formulations were bioequivalent with respect to $AUC_{0-\infty}$ and C_{max}, as were the lyophilized formulations from the crossover and rechallenge phases.
- A significant relationship between aPTT and plasma concentration was evident in each subject during and following administration of each formulation.

CONCLUSIONS

- Both formulations, frozen and lyophilized, were well-tolerated at these doses.
- The formulations were considered bioequivalent.
- aPTT directly correlated with plasma concentrations of BG8967.
- All assays for antibody to BG8967 were negative.
- Repeat exposure to BG8967 was well-tolerated and not associated with antibody formation.

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STUDY SYNOPSIS
Study Number C93-313

A Pharmacokinetic and Pharmacodynamic Study of BG8967 in Subjects with Renal Insufficiency

INVESTIGATOR

- Domenic A Sica, MD, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

OBJECTIVES

- The primary objectives of this study were to determine the safety, and the pharmacokinetic and pharmacodynamic profiles of BG8967 when administered to subjects with varying degrees of renal insufficiency as compared to healthy subjects.
- The secondary objective was to determine the pharmacokinetics and pharmacodynamics of BG8967 when administered during dialysis.

STUDY DESIGN

- Open label, parallel group in healthy subjects, subjects with mild, moderate or severe renal impairment, and dialysis-dependent subjects.
- Up to 8 subjects in each group.
- Six of the 8 dialysis-dependent subjects received 2 infusions: one on an "off dialysis" day, the other during dialysis.
- Subjects who did not complete the infusion due to prolonged coagulation times could receive an additional infusion at a half dose (0.25 mg/kg/h).
- Blood drawn during infusion and the 24 hour period after infusion for determination of plasma concentrations of BG8967 and aPTT or ACT.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.

TEST DRUG SCHEDULE

- BG8967 infused for 4 hours at a rate of 0.5 mg/kg/h.

POPULATION

- Healthy subjects with a glomerular filtration rate (GFR) of at least 90 mL/min/1.73m^2.
- Subjects with mild renal insufficiency with a GFR of 60-89 mL/min/1.73m^2
- Subjects with moderate renal insufficiency with a GFR of 30-59 mL/min/1.73m^2.
- Subjects with severe renal insufficiency with a GFR of less than 30 mL/min/1.73m^2.
- Dialysis-dependent subjects requiring maintenance hemodialysis at least twice per week.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS

- 39 subjects, 25 male, 14 female, aged between 21 and 73, were recruited and dosed with BG8967.
- 10 subjects in the groups with severe renal impairment and severe disease requiring hemodialysis had aPTT over 105 seconds; 5 were infused with a reduced dose.
- Mean pharmacokinetic and pharmacodynamic parameters were

	Normal Renal Function (n=8)	Mild Renal Impairment (n=8)	Moderate Renal Impairment (n=7)	– Severe Renal Impairment – 0.5 mg/kg/h (n=8)	0.25 mg/kg/h (n=2)	– Dialysis-dependent – Off Dia. 0.5 mg/kg/h (n=8)	Off Dia. 0.25 mg/kg/h (n=4)
Pharmacokinetic Parameters:							
$t_{1/2}$ (h)	2.7	3.5	3.7	3.3	4.0	3.7	3.8
C_{max} (ng/mL)	2110.3	2495.8	4026.0	6161.3	2149.0	5397.4	3135.8
$AUC_{0-\infty}$ (h.ng/mL)	7610.5	9245.9	18473.1	29225.6	13613.3	37874.2	21708.3
Half-life (h)	0.52	0.68	1.49	2.03	2.90	3.53	3.18
Clearance (mL/min/kg)	4.58	4.94	2.50	1.46	1.57	1.04	0.92
Vd (L/kg)	0.20	0.22	0.23	0.20	0.22	0.27	0.19
aPTT:							
$t_{1/2}$ (h)	2.7	2.7	2.7	2.7	3.0	3.6	3.2
E_{max} (sec)	58.3	44.7	56.8	79.4	57.1	84.4	54.2
E_{ave} (h.sec)	237.8	180.6	245.3	364.9	279.2	478.5	306.7

- Mean pharmacokinetic parameters in dialysis-dependent subjects (n=6) while on dialysis were

t_{max} (h)	3.7
C_{max} (ng/mL)	3154.3
$AUC_{0-\infty}$ (h.ng/mL)	15262.9
Half-life (h)	1.26
Clearance (mL/min/kg)	2.29
Vd (L/kg)	0.25

- Strong correlations between pharmacokinetic and pharmacodynamic parameters and measures of renal failure: C_{max}, AUC, E_{max}, E_{AUC} increase with the degree of renal impairment.
- BG8967 was dialysable.
- Very few adverse events were noted, the most common being vasodilatation (1 out of the 8 subjects with severe renal impairment, and 1 of the 8 subjects requiring dialysis), and rhinitis (1 of the 7 subjects with mild renal impairment, and 1 of the 6 subjects while on dialysis).

CONCLUSIONS

- BG8967 was well tolerated in subjects with renal insufficiency. There was a consistent prolongation of aPTT in association with drug administration, and a strong positive correlation between aPTT and plasma BG8967 concentration. Pharmacokinetic and pharmacodynamic profiles were similar among subjects with no renal impairment and mild renal impairment. In subjects with moderate renal impairment and, in particular, severe renal failure there was a tendency towards decreased BG8967 clearance and, thereby, increased pharmacodynamic effect. Dosage adjustment of BG8967 consistent with pharmacodynamic effect would seem indicated in patients with moderate and severe renal failure. Moreover, BG8967 appears to be dialysable and, during dialysis, may require a step-up of an existing infusion rate if an established level of anticoagulation is to be maintained.

APPEARS THIS WAY
ON ORIGINAL

STUDY SYNOPSIS
Study Number C93-316

A Double-Blind, Randomized, Crossover Study to Determine the Tolerability and to Compare the Pharmacokinetic Profiles of BG8967 Injection Prepared Using Homogeneous-Phase Pilot Chemistry *versus* Homogeneous-Phase Commercial Chemistry

INVESTIGATOR
- Dr. T.G.K. Mant, Guy's Drug Research Unit, Ltd., London, U.K.

OBJECTIVES
- To determine the tolerability and estimate the pharmacokinetic profiles of pilot chemistry frozen formulation BG8967 and commercial chemistry lyophilized formulation BG8967.
- To compare the BG8967 produced by these two methods.
- To correlate plasma drug levels with activated partial thromboplastin time (aPTT).

STUDY DESIGN
- Double-blind, randomized, two-period, two-treatment crossover in healthy male volunteers.
- Subjects randomized into one of two treatment sequences.
- Blood drawn during infusion and the 24 hour period after infusion for determination of plasma concentrations of BG8967 and aPTT.
- Urine collected during infusion and the 24 hour period after infusion for determination of concentrations of BG8967 in urine.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.

TEST DRUG SCHEDULE
- Two formulations of BG8967 injection: one frozen formulation prepared from pilot chemistry BG8967, one lyophilized formulation prepared from commercial chemistry BG8967.
- Each subject received each formulation once in a random order, with each infusion separated by 7 days.
- BG8967 infused for 4 hours at a rate of 0.5 mg/kg/h.

POPULATION
- Healthy male subjects.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS
- Twenty male caucasians, aged between 22 and 33 years, were enrolled and randomized into the study.
- Two subjects were incorrectly dosed, and were then withdrawn.
- Nine subjects in each treatment sequence received both pilot and commercial chemistry BG8967.
- Plasma drug concentration assay failed due to mechanical difficulties with the air conditioning system during higher than usual environmental temperatures. BG8967 is not stable in urine under the conditions used in this study for collection.
- From the aPTT-time curves, during and following infusion, the maximum change from baseline, E_{max}, and the area under the aPTT-time curve, E_{AUC}, were

	Pilot chemistry	Commercial chemistry
E_{max} (sec)	58.5	59.5
E_{AUC} (h.sec)	219.6	241.4

- Both formulations were considered equivalent with respect to aPTT.
- Very few subjects had adverse events: only headache and diarrhea were noted.

CONCLUSIONS
- Formulations of BG8967 prepared from pilot and commercial chemistries of BG8967 are equivalent.
- Formulations prepared from both chemistries were well-tolerated.

STUDY SYNOPSIS
Study Number C93-317

An Open-label, Randomized, Crossover Study in Healthy Volunteers to Evaluate the Interaction of BG8967 and Heparin

INVESTIGATOR

- Dr. T.G.K. Mant, Guy's Drug Research Unit, Ltd., London, U.K.

OBJECTIVES

- To determine and compare the tolerability and pharmacokinetic profiles of BG8967 when given either immediately after or immediately before treatment with heparin.
- To correlate plasma BG8967 levels with activated partial thromboplastin time (aPTT), and to evaluate the pharmacokinetic profile of heparin when administered serially with BG8967.

STUDY DESIGN

- Open-label, randomized, two-period crossover in healthy male volunteers.
- Subjects randomized into one of two dosing sequences:

	Period 1	*Period 2*
Sequence A:	Heparin then BG8967	BG8967 then Heparin
Sequence B:	BG8967 then Heparin	Heparin then BG8967

- Blood drawn during and after infusion for determination of plasma concentrations of BG8967, [redacted] assays to estimate plasma heparin levels.
- The protocol allowed for changes to heparin and/or BG8967 dosing regimens based on aPTT, which was not allowed to exceed 90 sec.
- Urine collected during infusion and the 24 hour period after infusion for determination of concentrations of BG8967 in urine.
- Safety monitored by vital signs, physical examination, blood chemistry, hematology, urinalysis and adverse event reporting.

TEST DRUG SCHEDULE

- Each subject received, in random order, BG8967 immediately followed by heparin in one treatment period, and heparin immediately followed by BG8967 in the other treatment period. Treatment periods were separated by 7 days.
- BG8967 infused for 4 hours at a rate of 0.25 mg/kg/h.
- Heparin administered by IV bolus (35 U/kg), then infused for 4 hours at a rate of 15 U/kg/h. Protocol update eliminated the need for the IV bolus.

POPULATION

- Healthy male subjects.
- Major exclusion criteria: active or prior history of bleeding tendencies, history of clotting disorders, history of cardiovascular and/or peripheral vascular disease, stroke or transient ischemic attack.

RESULTS

- Twelve males, aged between 23 and 34, were enrolled into the study. Six subjects were randomized into each dosing sequence.
- The first subject to be dosed received an IV bolus of heparin, followed by an IV infusion of heparin, followed by an IV infusion of BG8967. aPTT was elevated during the heparin and BG8967 infusions and the latter infusion curtailed. No other subject received IV boluses of heparin.
- Based on study C90-010, a one-compartment model was developed to predict plasma concentration-time curves of BG8967 and heparin.
- The antithrombotic effects (E) of both heparin and BG8967 are related to their respective plasma concentrations based on the equation $E=BC^{\gamma}$.
- The model prediction was consistent with the actual data points during the BG8967-heparin schedule.
- The model prediction was less consistent with the data during the heparin-BG8967 schedule.

CONCLUSIONS

- When instantaneously switching between therapeutic doses of heparin and BG8967 adequate and safe anticoagulation is maintained.
- Heparin bolus dosing is not necessary when switching from BG8967 to heparin.

STUDY SYNOPSIS
Study Number C93-317

- When switching from heparin to BG8967 a transient overshoot of anticipate [redacted] is seen. This can be prevented by allowing a 30 minute interval between discontinuation of BG8967 and initiation of heparin.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

STUDY SYNOPSIS
Study Number C94-321

The Antihemostatic Effects of BG8967 in Subjects with Renal Failure Treated with Chronic Hemodialysis

INVESTIGATOR

- L A Harker, MD, Emory University School of Medicine, Atlanta, GA

OBJECTIVE

- To determine the antihemostatic dose-response effects of BG8967 in renal failure subjects treated with chronic hemodialysis. This study was to define a safe and effective regimen for use in testing the hypothesis that BG8967 prevents failure of arteriovenous vascular (AV) access grafts in dialysis patients.

STUDY DESIGN

- Open-label, single center.
- Five groups of two to five subjects were dosed in three stages: an initial iv bolus, then 45 minutes later an iv infusion for 4 hours followed by sc administration for 24 hours.
- Coagulation times measured.
- In two groups, ^{111}Ind-platelets were reinfused with periodic γ-images of the AV graft taken.
- Subjects underwent follow-up hemodialysis.
- Some subjects were dosed more than once, in different groups.

TEST DRUG SCHEDULE

- Group 1: 0.1 mg/kg iv bolus, 0.5 mg/kg/h iv infusion for 4h, 1 mg/kg sc injection q8h for 24h.
- Group 2: 0.2 mg/kg iv bolus, 1.0 mg/kg/h iv infusion for 4h, 2 mg/kg sc injection q8h for 24h.
- Group 3: 0.05 mg/kg iv bolus, 0.25 mg/kg/h iv infusion for 4h, 0.5 mg/kg sc injection q8h for 24h.
- Group 4: 0.2 mg/kg iv bolus, 1.0 mg/kg/h iv infusion for 4h, 2 mg/kg sc injection q8h for 24h (^{111}Ind-platelets).
- Group 5: 0.5 mg/kg iv bolus, 2.0 mg/kg/h iv infusion for 4h, 0.5 mg/kg/h sc infusion for 24h (^{111}Ind-platelets).

POPULATION

- Clinically and biochemically stable on regular and adequate hemodialysis.
- No hypertension, bleeding problems, significant confounding diseases or therapies.
- Subjects were excluded with cerebral vascular event within prior two months, history of gastrointestinal bleeding in the past year, known coagulopathy or therapy with oral anticoagulants or aspirin.

RESULTS

- 8 males, 3 females, 30 to 73 years of age, were dosed. Six subjects were dosed once, four were dosed twice, and one was dosed three times.
- There were 5 subjects in Group 1; 4 and 2 subjects in Groups 2 and 4 respectively, and 3 subjects in each of Groups 3 and 5.
- All subjects completed; none were withdrawn.
- One patient died of cancer eight months after dosing. This was not considered to be related to BG8967.

- Mean aPTT in the groups was as follows:

Group	*3*	*1*	*2 and 4*	*5*
iv bolus (mg/kg)	*0.05*	*0.1*	*0.2*	*0.5*
Pre-dose	25.0	25.8	26.1	25.6
5 min	41.3	53.8	61.0	83.8
10 min	38.1	47.4	54.2	78.0
20 min	35.3	44.2	42.3	68.0
30 min	31.3	39.7	43.0	57.0
45 min	30.6	36.4	40.2	55.0
iv infusion (mg/kg/h)	*0.25*	*0.5*	*2.0*	*2.0*
2 h	54.7	69.9	94.8	115.0
4 h	66.0	88.9	124.1	167.0
sc injection (mg/kg)	*0.5*	*1.0*	*2.0*	-
1st injection				
Pre-dose	27.2	32.6	36.2	-
2 h	58.1	71.3	84.0	-
4 h	49.0	62.7	78.0	-
8 h	33.9	55.0	55.0	-
2nd injection				
2 h	51.1	-	85.6	-
4 h	50.0	57.8	75.4	-
6 h	-	-	69.4	-
8 h	34.8	43.8	55.0	-
3rd injection				
1 h	53.5	55.7	85.4	-
2 h	52.5	-	90.1	-
4 h	47.5	65.4	82.7	-
6 h	42.2	-	-	-
8 h	31.0	43.4	57.3	-

CONCLUSIONS

- In patients with chronic renal failure who are on dialysis, administration of BG8967 by iv bolus, continuous iv infusion or repeated subcutaneous injection results in a predictable dose-related effect on aPTT.
- BG8967 was well tolerated in this population.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-873
Bivalirudin Injection

Submission Date:
January 31, 1998
February 25 , 1998
March 25, 1998
May 11, 1998

MAY 26 1998

BRAND NAME: HIRULOG®

SPONSOR: Medicines Company
Cambridge, MA
(Regulatory Liaison: Quintiles Inc.)

REVIEWER: Arzu Selen, Ph.D.

TYPE OF SUBMISSION: Amendments to NDA

Code: 1S

The objectives of this review are to provide an overview of all of the amendments to date, respond to the Sponsor's amendments (dated February 25 and March 25, 1998) and provide an update on the status of all of the questions raised in the two FDA letters dated February 11, 1998 and March 17, 1998.

The first amendment (dated January 31, 1998), was submitted by the Sponsor prior to communication of the comments raised during the NDA 45 Day Filing Review. This amendment consisted of CMC stability data and a diskette of individual plasma bivalirudin concentrations obtained from Hirulog pharmacokinetic studies (C90-010, C90-041, C91-016, C92-305, C92-306, C93-310, C93-313, and C93-317). It was indicated that C91-016, included on the diskette, had not been included in the NDA..

The items noted during the 45-Day Filing Review of the Hirulog (bivalirudin) NDA submission, such as issues related to analytical methods, calculation of pharmacokinetic parameters, data interpretation (such as period and formulation interaction), evaluation of drug-drug interactions, and dose-adjustment in renal impairment (recommended in summary documents but not reflected in the proposed package insert) were communicated to the Sponsor in the FDA letter dated February 11, 1998.

In Sponsor's February 25, 1998 response, some of these items were addressed while others were acknowledged by the Sponsor as outstanding and feedback was requested for one of the items, that is use of mitochondria in in vitro assessment of potential drug-drug interactions with bivalirudin. The FDA's response to this amendment was on March 17, 1998.

On March 24, 1998, the Sponsor provided via fax a copy of a published article as the proposed study design for the in vitro drug-drug interaction study (1). In this article, inhibition of activity of cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6, 2E1, and 3A) by several protease inhibitors was evaluated. The substrate and the respective positive controls (inhibitors) used in this publication were phenacetin (1A2) and [redacted] tolbutamide (2C9) and [redacted] and omeprazole, dextromethorphan (2D6) and

quinidine and fluoxetine (positive controls), desipramine (2D6) and quinidine, chlorzoxazone (2E1) and [redacted] triazolam (3A) and ketoconazole. The proposed study design with emphasis on use of positive controls was considered acceptable and this was communicated to Ms. Julienne DuBeau, the Consumer Safety Officer, on March 24, 1998. The hard copy of this article was filed by the Sponsor as an amendment (dated May 11, 1998) related to issues raised in the FDA February 11, 1998 letter.

The Sponsor submitted a third amendment, dated March 25, 1998, to address some of the remaining issues raised in the FDA February 11, 1998 letter.

The status of the items, Items D1 through D10, as identified in the FDA February 11, 1998 letter to the Sponsor, are listed in the following section with the pertinent responses from the Sponsor in the three amendments dated February 25, March 25, and May 11, 1998. These amendments are in Appendices 1, 2 and 3.

The comments that need to be communicated to the Sponsor are listed under comments to be communicated to the Sponsor.

THE STATUS OF ITEMS THAT HAVE BEEN COMMUNICATED TO THE SPONSOR:

1. **Item D1:**
   Assay validation and related information for each study, preparation and performance of quality control samples, raw data (including data utilized to construct calibration curves), stability of bivalirudin in samples, freeze-thaw stability, sample storage conditions as well as information and supporting raw data were requested.

   Status: Outstanding.
   In their March 25, 1998 dated letter, the Sponsor indicated that the analytical report(s) addressing the issues raised in this item will be submitted in June.

   Further action: Additional questions related to assay method development, the specificity of the antibody, lack of use of quality control standards in all studies (although implied in the assay validation report), and other method related issues were also identified as issues to be communicated to the Sponsor in the Clinical Pharmacology and Biopharmaceutics review dated April 30, 1998.

2. **Item D2:**
   A tabulated summary listing assay method, validated analytical range, the dates of assay validation and sample analysis for each Hirulog® study was requested.

   Status: Outstanding.
   In their March 25, 1998 dated letter, the Sponsor indicated that the analytical report(s) addressing the issues raised in this item will be submitted in June.

   Further action: None at this time.