

3. Item D3:

Information on the methods and equipment used for aPTT measurements by study and the site where measurements were made as well as how the equipment was calibrated was requested from the Sponsor.

Status: Outstanding.

In their March 25, 1998 dated letter, and the fax dated March 22, 1998 (included in the May 11, 1998 amendment), the Sponsor indicated that this issue will be addressed by May 1.

Further action: The Sponsor has not provided this information as of May 21, 1998 and will be requested to submit this information under the comments to be communicated to the Sponsor.

4. Item D4:

It was noted that in C93-310, although plasma bivalirudin concentrations in almost all of the subjects were below the limit of quantification by 6 h after the start of infusion, the Sponsor had provided AUC(0-28) values. Instead of AUC(0-28), the Sponsor was requested to recalculate area under drug concentration-time curve from time zero to time of last detectable concentrations (AUC(0-t)) and utilize these values to calculate AUC(0- ∞) values. Subsequently, the Sponsor would recalculate clearance as the ratio of dose to AUC(0- ∞) for C93-310.

Status: In the February 25, 1998 response, the Sponsor provided a list of recalculated AUC(0-t), AUC(0- ∞) and clearance values. As expected the AUC values were lower than the values provided in the NDA. The differences between the AUC(0-t) values recalculated by the Sponsor and randomly selected and recalculated by the reviewer were small (mostly < 1%). The Sponsor's response was accepted (FDA letter dated March 17, 1988).

However, a subsequent closer review of all of the data indicated that the AUC(0-t) calculations may include an additional area from the last detectable concentration to a zero value at the next sampling time. All of the AUC(0-t), AUC(0- ∞) and clearance values for this study were recalculated by the reviewer. The AUC values listed in the NDA, recalculated by _____ and the reviewer are compared in the following tables, Table 1 and Table 2 for the frozen and lyophilized formulations, respectively.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1: Comparison of individual AUC values obtained following administration of the frozen formulation of Hirulog to healthy volunteers. (C93-310)

Subject No.	As submitted in the NDA	Recalculated by ~~_____~~		Calculated by the reviewer	
	AUC(0-28) (ng.h/ml)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)
101	7015.9	6807.4	6997.67	6827.95	7091.94
102	5326.96	5134.56	5469.4	5146.51	5481.35
103	5708.19	5505.58	5825.2	5512.79	5832.41
104	6248.99	6018.72	6368.39	6030.94	6380.61
105	5195.21	5010.23	5419.43	5020.71	5282.16
106	5471.84	5281.31	5633.51	5290.84	5578.35
108	6607.18	6344.15	6827.94	6352.38	6802.79
109	4125.19	3936.97	5341.58	3952.59	4545.24
110	7417.18	7099.79	7753.18	7114.68	7768.06
111	6250.58	6052.56	6305.07	6065.08	6317.59
112	5115.44	4974.4	5154.57	4984.64	5164.8
113	2036.4	1947.57	Not calculated	Not calculated	Not calculated
114	5769.83	5553.11	5857.37	5582.68	5861.93
115	6649.25	6402.11	6721.36	6409.45	6809.55
Mean	5638 (n=14)	5434 (n=14)	6129 (n=13)	5715 (n=13)	6071 (n=13)
CV%	23.9%	24%	12.7%	15.1%	14.8%

Note: 1) Subject 7 did not receive the frozen Hirulog formulation

2) The AUC(0-28) values were considered to be equivalent to AUC(0-inf) in the original NDA except for Subject 13. Subject 13's AUC(0-28) value, as listed in the NDA was included in calculation of the mean AUC(0-28) but was not used for calculation of AUC(0-inf).

3) The mean AUC(0-last) value, based on parameters recalculated by ~~_____~~ for 13 subjects (excluding the AUC value of Subject 13) is 5702 ng.h/ml with a CV% of 15.2%.

APPEARS THIS WAY
ON ORIGINAL

Table 2: Comparison of individual AUC values obtained following administration of the lyophilized formulation of Hirulog to healthy volunteers. (C93-310)

Subject No.	As submitted in the NDA	Recalculated by _____		Calculated by the reviewer	
	AUC(0-28) (ng.h/ml)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)
101	7597.41	7392.96	7634.91	7416.81	7658.77
102	5985.68	5787.17	6046.46	5810.77	6054.2
103	5019.01	4782.2	5463.71	4791.46	5472.97
104	6347.78	6144.08	6398.1	6155.57	6384.18
105	8033.75	7800.66	8056.77	7823.45	8079.56
106	6663.4	6448.69	6774.16	6464.65	6790.11
107	8590.57 and 9032.79-	Not reported	Not reported	17337.38	43215.47
108	5690.58	5428.22	5888.30	5445.48	5906.44
109	5925.86	5677.34	6126.62	5686.26	6135.54
110	8378.43	8002.74	8393.26	8037.73	8449.27
111	6191.79	6036.13	6197.77	6054.44	6216.08
112	4263.91	4217.03	4385.42	4227.51	4395.9
113	1772.85	1699.18	Not calculated	Not calculated	Not calculated
114	7155.66	6879.24	7196.8	6906.86	7153.08
115	7808.27	7470.15	8244.14	7488.51	8262.50
Mean	6202 (n=14)	5983 (n=14)	6677 (n=13)	6332 (n=13)	6689 (n=13)
CV%	26.9%	27.8%	17.7%	18.5%	17.8%

Note:1) For Subject 7, in the NDA, the AUC(0-28) and AUC(0-∞) values, as listed above, are 8590.57 ng.h/ml and 9032.79 ng.h/ml, respectively. The Sponsor appears to have subtracted the value observed at time zero (314.1 ng/ml) from all of the samples for calculation of AUC(0-28) and AUC(0-inf) values.

2) The AUC values calculated by the reviewer for this subject are not included in calculation of the mean values.

3) The mean AUC(0-tlast) value, based on parameters recalculated by _____ for 13 subjects (excluding the AUC value of Subject 13) is 6313 ng.h/ml with a CV% of 18.4%.

4) The AUC values calculated for Subject 7 were not used by the reviewer in calculation of the mean values.

Although, for most subjects, small differences were noted between the recalculated AUC values submitted by _____ (February 25, 1998) and the AUC values calculated by the reviewer, the recalculated clearance values submitted by _____ in the February 25, 1998 amendment were considerably higher than the clearance values reported in the NDA or calculated by the reviewer. This indicates that either the clearance calculations in the amendment or the administered dose given in the study report are incorrect.

Further action: The inaccuracies in AUC(0-t) and subsequently in AUC(0-inf) and the clearance values need to be communicated to the Sponsor. The differences noted in these values necessitate verification of calculations in all the other studies. All of these issues are listed under comments to be communicated to the Sponsor.

5. Item D5:

The Sponsor was requested to provide their assessment of possible contributing factors of period effect and period and treatment interaction observed in Study C93-310.

Status: In the February 25, 1998 response from the Sponsor, it was indicated that there were no apparent reasons that could explain the period and period and treatment interaction effects observed in this study, C93-310.

In the FDA letter dated March 17, the Sponsor was requested to repeat bioequivalence assessment with the recalculated AUC values [AUC(0-tlast) and AUC(0-∞)] from C93-310. In addition, for further exploration of the period and treatment (formulation) interaction, the Sponsor was asked to submit an ASCII file of the bivalirudin parameters [Cmax, AUC values reported in the study report (AUC(0-28) and AUC(0-∞)) and the recalculated AUC values (AUC(0-tlast), and AUC(0-∞))] for each subject with their formulation, period and sequence information on a diskette to the Agency.

Following evaluation of the data submitted in the NDA and the Sponsor's February 25, 1998 response, the period and treatment interaction effect is traced to contribution of data from one of the volunteers (Subject #13). The plasma bivalirudin concentrations for this subject are reported to be undetectable in samples collected up to 1 h after the start of bivalirudin infusion as well as in all samples collected after infusion, including the 15 min sample after the end of infusion. For both formulations, the Sponsor had utilized the plasma concentrations of bivalirudin detected at 1, 2 and 4 h after the start of Hirulog infusion, for calculation of AUC(0-28) as reported in the original NDA and as AUC(0-t) in the February 25, 1998 amendment. The contribution of this subject's AUC values, in addition to being inaccurate representation of the AUC(0-tlast), has resulted in the period and treatment interaction effect observed in the AUC(0-tlast) values. Because there was no AUC(0-∞) value calculated for this volunteer, there were no statistically significant ($p < 0.05$) period or period and treatment (formulation) interaction effects in the AUC(0-∞) values.

In addition, it was also noted that although SAS GLM procedure was used, the Sponsor had excluded the data from Subject 7 from statistical analysis. Subject 7 had received only the lyophilized formulation and had detectable bivalirudin concentrations even before administration of the Hirulog dose. Plasma bivalirudin concentrations for this subject remained over the quantification level even at the last sample collection time, 28 h after initiation of the infusion dose. This observation is somewhat consistent with the information provided in Assay Validation Report in Section 6, suggesting possible interference of endogenous substances with the assay as detectable bivalirudin concentrations were obtained in the plasma of at least 5 of 9 randomly selected volunteers who had not received Hirulog. These results suggest that the data obtained for Subject 13 may also be due to less than optimal assay conditions as well as possible improper sample handling.

Reanalysis of the data by excluding the data from Subjects 7 and 13 by the reviewer, if the aberrant nature of data from these subjects could be attributed to assay or analytical procedures, shows that there are no statistically significant period and treatment interactions in any one of the parameters (Appendix 4). Although the Sponsor has not identified the contribution of Subject 13's data for the observed period and period and treatment interaction effects, the contribution of this subject's data is considered to be the reason of the observed period and treatment interaction effects.

In Table 3, the 90% confidence intervals for the ratios of the AUC values calculated by the reviewer are compared with the values provided in the Sponsor's March 25, 1998 response. Although there are small differences, both sets of AUC values support the bioequivalence of the lyophilized formulation to the frozen formulation of bivalirudin as the 90% C. I. of the ratios of log-transformed parameters are within the acceptance criteria of 80%-125%.

Table 3: Comparison of 90% confidence intervals calculated for bivalirudin AUC values obtained after administration of frozen and liquid Hirulog formulations, C93-310.

Parameter	90% C.I as recalculated by _____ (n=14 for AUC(0-t) and n=13 for AUC(0-∞))	90% C.I. as calculated by the reviewer (n=13)
AUC(0-t) ng.h/ml	100 - 114%	101 - 120%
AUC(0-∞) ng.h/ml	97.9 - 113%	102 - 118%

Further action: The assay related issues and the other issues noted during review of C93-310 are listed below. The items that need to be communicated to the Sponsor are also listed in the section, .

- 1) The Sponsor needs to address the detectable plasma concentrations of bivalirudin in plasma sample collected before the Hirulog dose (Subject 7) and how detectable concentrations are maintained up to 28 h postdose (the last sample collected according to study protocol) in this subject.. The analytical interference or sample handling has not been addressed.
- 2) Subject 13 had detectable plasma bivalirudin concentrations in samples collected at 1, 2 and 4 h during infusion. The bivalirudin plasma concentrations were below the limit of quantification (<235 ng/ml) in 0.25 and 0.5 h samples after the start of infusion and in all samples collected after the end of infusion, such as even the 15 min sample after the end of infusion. This observation suggests analytical or procedural issues and should have been further verified by repeated analysis of samples and/or further investigation of other possible contributing factors.
- 3) Inclusion of the data from Subject 13 results in the observed period and treatment interaction in AUC(0-28) or in the AUC(0-tlast) values which the Sponsor may have identified when this question was raised in the FDA February 11, 1998 letter.

Although reanalysis of the parameter sets recalculated either by _____ or by the reviewer shows that the two formulations are bioequivalent, given the assay related issues, validity of this bioequivalence study is considered questionable. The Sponsor

may address some of these issues in their later submissions, however, at this time, the assay method in the report is inconsistent with the assay validation report in Section 6 suggesting that assay used for analysis of samples from this bioequivalence study was not validated. In addition, according to the study report (Vol 1.044, pages 15 and 16), there were no quality control samples assayed during analysis of samples from this study, and the data from Subjects 7 and 13 suggest that there were fundamental analytical and/or procedural issues that were not addressed.

These comments are also reflected under the section for comments to be communicated to the Sponsor.

6- Item D6:

The Sponsor was requested to provide a list of bridging studies to accommodate the major manufacturing and formulation changes with lot numbers of the formulations used, a description of the major changes, methods, dates of study conduct, report numbers and their location in the NDA submission.

Status: In their March 25, 1998 response, the Sponsor has provided a list of three studies which were considered to be the bridging studies conducted during development of Hirulog formulations. These studies are C92-305, C93-310 and C93-316 for comparison of frozen formulation of Hirulog to the refrigerated formulation (C92-305), frozen liquid formulation to the lyophilized formulation (C93-310), and finally, comparison of frozen liquid formulation made by pilot scale chemistry process to lyophilized formulation manufactured by commercial scale process (C93-316). Of these studies, plasma bivalirudin measurements are available only from studies C92-305 and C93-310.

The Hirulog formulations evaluated in the clinical efficacy and safety trials, were frozen liquid formulation prepared by solid phase synthesis (C90-041) and frozen liquid formulation prepared by liquid phase pilot scale synthesis (C92-304-1 and C92-304-2), while the desired to be marketed product is the lyophilized formulation manufactured at commercial scale. Although Study C93-316 was conducted to assess the bioequivalence of the lyophilized formulation manufactured at commercial scale against the frozen liquid formulation, because of analytical/technical difficulties, samples from this study could not be assayed and Study C93-310 has been submitted as the pivotal bioequivalence study to evaluate the frozen and the lyophilized Hirulog formulations.

As requested, the Sponsor has provided the drug substance batch and finished product lot numbers for the Hirulog finished products used in the three studies. Since bivalirudin pharmacokinetics were evaluated in the 2 studies (C92-305 and C93-310), the manufacturing dates for the finished product (obtained from January 31, 1998 amendment) and the study conduct dates (obtained from March 25, 1998 amendment) are listed in the following table, Table 4.

Table 4: The Hirulog finished products used in bridging studies, their manufacture and study conduct dates.

Finished Product Lot Numbers (Study number))	Manufacture date	Study conduct dates
67Z01S (C93-310)	January 13, 1993	5/12/93 -10/28/93
67Z04S (C93-310)	March 11, 1993	
67X15W (C92-305)	Could not be located	8/17/92-9/22/92
67Y01Z (C92-305)	July 1, 1992	

Although the Sponsor had not provided expiration dates, given the timings of study dates with respect to manufacturing dates, except for Lot 67X15W, it appears that there should be no apparent stability issues. Information on Lot 67X15W could not be located in the CMC stability listing and this information will be requested from the Sponsor.

The dates provided for these studies and the date of the assay validation report suggest that at least for study C92-305, the samples were either assayed by a non-validated method or stored for a considerable period. Because the response to Item D1 is not yet available, it is not possible to determine when the samples from the bridging studies were assayed.

Further action: Manufacturing date for Lot 67X15W will be requested from the Sponsor.

7. Item D7:

The Sponsor was requested to clarify whether the reference made to an in vitro metabolism study in which rat hepatocytes were used for assessment of potential drug-drug interactions with p450 isozymes was based on the P8967-92-08 study report. If not, the Sponsor was requested to provide the study report number for the report being referred to and its location in the NDA submission.

Status: In February 25, 1998 response, the Sponsor has indicated that the referred study was P8967-94-06 in Volume 1.034, page 245.

Following review of the report in Volume 1.034, on page 245, it was noted that the study referred to two Biogen studies (P8967-94-02, 28-day toxicology study and P8967-94-06, in vitro study).

In the March 17 FDA letter, the Sponsor was requested to provide the dosing information (preparation of dosing solution, verification of concentration of bivalirudin in dose solution, conditions of storage of bivalirudin and the dosing vehicle and stability of bivalirudin in the dosing vehicle) and copies of the supporting documentation. Furthermore, the Sponsor was requested to verify whether the NOAEL dose in the rat, indicated to be 25 mg/kg/day, on page 123 of Volume 1.002 is accurate. Given the information presented on Panel 3.5.6B, page 124 of Volume 1.002, signs of liver damage observed after 28 days of iv infusion of bivalirudin, the Sponsor was asked whether the conclusion of lack of potential drug-drug interactions with bivalirudin, derived from the results of Study P8967-94-02 would be reliable.

In the March 25, 1998 response the Sponsor confirms that the Study Report P8967-94-02 refers to a 28 day continuous infusion study in the rats while the Study Report P8967-94-06 refers to the in vitro study. The rat liver microsomal fractions obtained from the 28-day study P8967-94-02 were utilized in Study P8967-94-06 to assess the effects of Hirulog on selected p450 enzymes. Although the Sponsor states in their response that this was not considered a drug interaction study, and states that "the results suggest that exposure to Hirulog is unlikely to affect the hepatic p450-mediated metabolism of other concomitant therapies" (March 25, 1998 amendment, page 9), however, in the NDA (Volume 1.002, page 51), it is stated that "Hirulog exhibits low potential for adverse interactions with concomitant therapies. Hirulog does not affect hepatic p450 isoenzyme activity and therefore, should not affect p450 metabolism of concomitantly administered drugs that are cleared by the liver".

As apparent in their recent response, the Sponsor seems to prefer to consider the results of this study (P8967-94-06) in a manner less definitive than that as stated in the NDA.

The study reports, including the pathologist's report, stability documents as well as certificates of analysis submitted in the March 25, 1998 were also reviewed and the response to the Sponsor for this Item, Item D7 are listed as comments to be communicated to the Sponsor.

Further Action: Several comments for clarification purposes are listed as comments to be communicated to the Sponsor.

8. Item D8:

To accommodate the original timelines (with a possible July Advisory Committee Meeting), the Sponsor was requested to provide an in vitro assessment of potential drug-drug interactions for bivalirudin utilizing human hepatocytes (for comparison with the preclinical data and claims) by April 1, 1998.

Status: Based on the proposed study protocol faxed on March 24, 1998 and the comment in the February 25, 1998 amendment, the Sponsor seems to have agreed to conduct an in vitro study to assess the potential of drug-drug interactions with bivalirudin.

Further Action: None until the study report is received.

9. Item D9:

The Sponsor was asked to clarify the duration of infusion in Panel 3.6.3.B. volume 1.002, page 150.

Status: The Sponsor provided the duration of infusion (4 h) which was incorrectly stated in Panel 3.6.3.B. Volume 1.002, page 50 and referred to the other sections in the NDA where the information was accurate.

Further action: No further action.

10. Item D10:

The Sponsor was asked to provide an explanation for omission of the recommended dose adjustment in patients with renal impairment in the proposed package insert as this recommendation was made in the text of the NDA.

Status: In their, March 25, 1998 response, the Sponsor has indicated that this item will be addressed later and is still outstanding.

Further Action: The Sponsor will be reminded that this item is still pending.

Other Request:

In the March 17, 1998 FDA letter, the Sponsor was also requested to provide ASCII files of all pharmacokinetic/pharmacodynamic parameters for each study on a diskette. These files will also include the appropriate formulation (and dose), sequence, period and demographic information for each subject.

Status: Outstanding

Further Action: The Sponsor will be reminded that this item is still pending.

COMMENTS TO BE COMMUNICATED TO THE SPONSOR:

1. The Sponsor needs to provide responses related to analytical issues in Items D1, D2, and D3 as requested in the FDA letter dated February 11, 1998.
2. Item D4: During more in depth review, errors were noted in the Sponsor's response to Item D4 which was specific for Study C93-310. The Sponsor needs to verify that AUC(0-t) values do not include an additional area calculated between the last detectable concentration and an assumed concentration of "zero" at the next sampling time. The Sponsor should also verify the clearance values provided in the February 25, 1998 amendment. It appears that either the doses listed in the C93-310 Study report (Volume 1.044, pages 180-186) or the clearances on page 4 of the amendment are incorrect. The Sponsor should provide a list of the dose and the AUC values used for calculation of the clearance parameters reported in the February 25, 1998 amendment.

In addition to C93-310, the Sponsor should verify all of the AUC and clearance calculations in all of the bivalirudin studies for further consideration of these studies. As requested in the FDA March 17, 1998 letter, the Sponsor should provide all formulation (and dose), sequence, period and demographic information as well as pharmacokinetic and pharmacodynamic parameters (if available) for all of the submitted bivalirudin studies.

3. Item D5: The Sponsor needs to address the detectable plasma concentrations of bivalirudin in the plasma sample collected before the Hirulog dose (Subject 7) and given that detectable concentrations of bivalirudin were maintained up to 28 h postdose (the last sample collected according to study protocol), how were the bivalirudin concentrations in these samples verified? The analytical interference and/or sample handling issues are expected to be covered in Items D1 and D2.

Similarly, results of Subject 13 suggest non-optimal analytical conditions, as detectable bivalirudin concentrations in plasma samples were observed only in samples collected at 1,

2 and 4 h after the start of infusion. What are the analytical or procedural issues that could have resulted in these observations and what was done to further investigate the possible contributing factors?

Inclusion of the data from Subject 13 seems to contribute to the observed period and treatment interaction in AUC(0-28) or in the AUC(0-tlast) values. Although reanalysis of the parameter sets recalculated either by or by the reviewer shows that the two formulations are bioequivalent, given the assay related issues, validity of this bioequivalence study is considered questionable.

The Sponsor needs to address assay related issues as soon as possible. The assay method in the study report is inconsistent with the assay validation report in Section 6 suggesting that assay used for analysis of samples from this bioequivalence study was not validated. In addition, according to the study report (Vol 1.044, pages 15 and 16), there were no quality control samples assayed during analysis of samples from this study, and the data from Subjects 7 and 13 suggest that there were fundamental analytical and/or procedural issues that need to be addressed.

4. Item D6: The Sponsor needs to provide manufacturing date for Lot 67X15W.
5. Item D7: Given the reported hepatic necrosis as stated in the pathologist's report of Study P8967-94-02 (NDA Volume 1.002, pages 125 and 126 and March 25 1998 Amendment, page 52), the microsomal fractions obtained from these animals and used in Study P8967-94-06 are not considered to be suitable to assess lack of effect of bivalirudin on p450 isoenzymes.

The reviewer's objections are to the following statement in the NDA (Volume 1.002, page 51) "Hirulog exhibits low potential for adverse interactions with concomitant therapies. Hirulog does not affect hepatic p450 isoenzyme activity and therefore, should not affect p450 metabolism of concomitantly administered drugs that are cleared by the liver" and the fact that Study P8967-94-06 was utilized to support this statement.

In the recent March 25, 1998 response, the Sponsor has stated that "the results (of Study P8967-94-06) suggest that exposure to Hirulog is unlikely to affect the hepatic p450-mediated metabolism of other concomitant therapies ". It is believed that the Sponsor currently does not have data to support such a claim and is advised to wait for the results of the proposed in vitro study.

6. The responses for Items D8 and D10 should be submitted to the Agency as soon as possible.
7. Item D9 is considered to be resolved.

Reference:

1. L.L. von Moltke, D.J. Greenblatt, J.M. Grassi, et al, "Protease Inhibitors as Inhibitors of Human Cytochromes p450: High Risk Associated with Ritonavir", J. Clin. Pharmacol, 38, 106-111, 1998.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the responses from Quintiles, Inc., dated February 25, 1998, March 25, and May 11, 1998. The outstanding items as well as the related follow-up comments are listed under the section, Comments to be Communicated to the Sponsor (pages 11 and 12 of this document). For timely completion of the clinical pharmacology and biopharmaceutics review of the NDA 20873, the Sponsor is requested to provide the information required as soon as possible to the Agency.

/S/

Arzu Selen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by /S/ 5/21/98
John Hunt, B.Sc.
Deputy Director and Acting Team Leader

FT initialed by /S/ 5/26/98
Mei-Ling Chen, Ph.D.
Director, DPE II

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

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
 Check creation of log-transformed parameters lnresp + transpose

OBS	SUBJECT	TREAT	PERIOD	SEQ	PARAMETE	ESTIMATE	LNRESP
1	101	F	1	FPL	AUCLAST	6807.40119124659	8.82577
2	101	F	1	FPL	AUCINF	6997.67476969161	8.85333
3	101	L	3	FPL	AUCLAST	7392.9565448737	8.90828
4	101	L	3	FPL	AUCINF	7634.91313619307	8.94049
5	102	F	2	PFL	AUCLAST	5134.56064178851	8.54375
6	102	F	2	PFL	AUCINF	5469.39566448523	8.60692
7	102	L	3	PFL	AUCLAST	5787.16879469814	8.66340
8	102	L	3	PFL	AUCINF	6046.45816127853	8.70723
9	103	F	3	LPF	AUCLAST	5505.67866099775	8.61352
10	103	F	3	LPF	AUCINF	5825.20049245582	8.66995
11	103	L	1	LPF	AUCLAST	4782.20484655757	8.47266
12	103	L	1	LPF	AUCINF	5463.70775158482	8.60588
13	104	F	2	LFP	AUCLAST	6018.71841007175	8.70263
14	104	F	2	LFP	AUCINF	6368.39399675468	8.75910
15	104	L	1	LFP	AUCLAST	6144.08118308279	8.72324
16	104	L	1	LFP	AUCINF	6398.10172208099	8.76376
17	105	F	1	FLP	AUCLAST	5010.23134809246	8.51924
18	105	F	1	FLP	AUCINF	5419.42650630852	8.59775
19	105	L	2	FLP	AUCLAST	7800.66471920288	8.96196
20	105	L	2	FLP	AUCINF	8056.77163555178	8.99427
21	106	F	3	PLF	AUCLAST	5281.30517042719	8.67193
22	106	F	3	PLF	AUCINF	5633.51000504725	8.63649
23	106	L	2	PLF	AUCLAST	6448.69272092921	8.77163
24	106	L	2	PLF	AUCINF	6774.15533752394	8.82087
25	108	F	1	FPL	AUCLAST	6344.15136633089	8.75529
26	108	F	1	FPL	AUCINF	6827.94328768362	8.82878
27	108	L	3	FPL	AUCLAST	5428.21918105338	8.59937
28	108	L	3	FPL	AUCINF	5888.29523485373	8.68072

Source:r:\common\shenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
 Check creation of log-transformed parameters lnresp + transpose

OBS	SUBJECT	TREAT	PERIOD	SEQ	PARAMETE	ESTIMATE	LNRESP
29	109	F	3	PLF	AUCLAST	3936.96979929862	8.27817
30	109	F	3	PLF	AUCINF	5341.67511385209	8.68328
31	109	L	2	PLF	AUCLAST	5677.341139581	8.64424
32	109	L	2	PLF	AUCINF	6126.61575053252	8.72040
33	110	F	1	FLP	AUCLAST	7099.79476989196	8.86782
34	110	F	1	FLP	AUCINF	7753.1786105148	8.95586
35	110	L	2	FLP	AUCLAST	8002.74199854794	8.98754
36	110	L	2	FLP	AUCINF	8393.25938539398	9.03518
37	111	F	2	PFL	AUCLAST	6052.65580671756	8.70824
38	111	F	2	PFL	AUCINF	6305.07101189412	8.74911
39	111	L	3	PFL	AUCLAST	6036.12917473562	8.70552
40	111	L	3	PFL	AUCINF	6197.77197251866	8.73195
41	112	F	2	LFP	AUCLAST	4974.40060473495	8.51206
42	112	F	2	LFP	AUCINF	5154.567451503	8.54764
43	112	L	1	LFP	AUCLAST	4217.03139513375	8.34689
44	112	L	1	LFP	AUCINF	4365.41981227093	8.38604
45	113	F	3	LPF	AUCLAST	1947.675	7.57434
46	113	F	3	LPF	AUCINF		
47	113	L	1	LPF	AUCLAST	1699.175	7.43790
48	113	L	1	LPF	AUCINF		
49	114	F	2	PFL	AUCLAST	5553.11127916574	8.62211
50	114	F	2	PFL	AUCINF	5857.3676782081	8.67546
51	114	L	3	PFL	AUCLAST	6879.23636059557	8.83626
52	114	L	3	PFL	AUCINF	7196.80212514913	8.88139
53	115	F	1	FLP	AUCLAST	6402.11421759044	8.76438
54	115	F	1	FLP	AUCINF	6721.35705472935	8.81305
55	115	L	2	FLP	AUCLAST	7470.15247015472	8.91867
56	115	L	2	FLP	AUCINF	8244.14219927813	9.01726

Source:r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
Check creation of log-transformed parameters lnresp + transpose

Analysis with treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCINF -----

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJECT	14	101 102 103 104 105 106 108 109 110 111 112 113 114 115
SEQ	6	FLP FPL LFP LPF PFL PLF
PERIOD	3	1 2 3
TREAT	2	F L

Number of observations in by group = 28

NOTE: Due to missing values, only 28 observations can be used in this analysis.

Source:r:\common\shenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
Check creation of log-transformed parameters lnresp + transpose

Analysis with treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCINF -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	17	0.56661074	0.03333004	4.04	0.0253
Error	8	0.06606235	0.00825779		
Corrected Total	25	0.63267308			

R-Square	C.V.	Root MSE	LNRESP Mean
0.895582	1.038258	0.09087240	8.75238982

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	5	0.27877780	0.05575556	6.75	0.0095
SUBJECT(SEQ)	7	0.16862173	0.02408882	2.92	0.0784
TREAT	1	0.03913597	0.03913597	4.74	0.0611
PERIOD	2	0.04382684	0.02191342	2.65	0.1306
PERIOD*TREAT	2	0.03624840	0.01812420	2.19	0.1738

Source: r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
 Analysis of Log-transformed Pharmacokinetic Parameters
 Check creation of log-transformed parameters lnresp + transpose

16:28 Monday, March 23, 1998

Analysis with treatment and period interaction

NAME OF FORMER VARIABLE=AUCINF

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.07385822	0.01477164	1.79	0.2214
SUBJECT(SEQ)	7	0.16862173	0.02408882	2.92	0.0784
TREAT	1	0.01424107	0.01424107	1.72	0.2255
PERIOD	2	0.05196222	0.02598111	3.16	0.0982
PERIOD*TREAT	2	0.03624840	0.01812420	2.19	0.1738

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.07385822	0.01477164	0.61	0.6948

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
L vs F	0.04998434	1.31	0.2255	0.03806226

Source: r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters
Check creation of log-transformed parameters lnresp + transpose

16:28 Monday, March 23, 1998

Analysis with treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCLAST -----

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJECT	14	101 102 103 104 105 106 108 109 110 111 112 113 114 115
SEQ	6	FLP FPL LFP LPF PFL PLF
PERIOD	3	1 2 3
TREAT	2	F L

Number of observations in by group = 28

Source:r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
Check creation of log-transformed parameters lnresp + transpose

Analysis with treatment and period interaction

NAME OF FORMER VARIABLE=AUCLAST

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	18	3.32930773	0.18462821	22.67	0.0001
Error	9	0.0732968E	0.00814409		
Corrected Total	27	3.39660458			

R-Square	C.V.	Root MSE	LNRESP Mean
0.978421	1.049196	0.09024464	8.60131424

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	5	1.82483373	0.36496675	44.81	0.0001
SUBJECT(SEQ)	8	1.28901905	0.16112738	19.78	0.0001
TREAT	1	0.04466593	0.04466593	5.48	0.0439
PERIOD	2	0.07493386	0.03746693	4.60	0.0420
PERIOD*TREAT	2	0.08985517	0.04492758	5.52	0.0273

Source:r:\common\shenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
 Analysis of Log-transformed Pharmacokinetic Parameters
 Check creation of log-transformed parameters lnresp + transpose

16:28 Monday, March 23, 1998

Analysis with treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCLAST -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.52666444	0.10533289	12.93	0.0007
SUBJECT(SEQ)	8	1.28901905	0.16112738	19.78	0.0001
TREAT	1	0.02884011	0.02884011	3.54	0.0925
PERIOD	2	0.08090710	0.04045355	4.97	0.0352
PERIOD*TREAT	2	0.08985517	0.04492758	5.52	0.0273

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.52666444	0.10533289	0.65	0.6679

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
L vs F	0.06485252	1.88	0.0925	0.03446274

Source:r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
 Analysis of Log-transformed Pharmacokinetic Parameters
 Check creation of log-transformed parameters lnresp + transpose

16:28 Monday, March 23, 1998

Analysis with treatment and period interaction

OBS	PARAMETE	_NAME_	TREAT	LSMEAN	STDERR	NUMBER	COV1	COV2	DF
1	AUCINF	LNRESP	L	8.75761	0.026933	2	.00000101	.00072537	8
2	AUCINF	LNRESP	F	8.70783	0.026933	1	.00072537	.00000101	8
3	AUCLAST	LNRESP	L	8.60759	0.024465	2	.00000471	.00059855	9
4	AUCLAST	LNRESP	F	8.54273	0.024465	1	.00059855	.00000471	9

APPEARS THIS WAY
 ON ORIGINAL

Source:r:\common\ahenry\medicine\glm1.sas (23MAR98) (16:28) (1)

APPEARS THIS WAY
 ON ORIGINAL

Medicine Co.
 Analysis of Log-transformed Pharmacokinetic Parameters
 95% C.I.'s for least squares treatment means and
 90% C.I.'s for differences between treatments
 Analysis with treatment and period interaction

16:28 Monday, March 23, 1998

OBS	PARAMETE	DIFF	LSMEANN1	LSMEAND1	SED	P	P1	P2	PROB	T
1	AUCINF	0.0499843	6358.8959585	6048.8636871	0.0380623	0.228	0.000	0.001	equiv	1.313
2	AUCLAST	0.0648525	6473.0208165	5129.3461355	0.0344627	0.093	0.000	0.001	equiv	1.882
OBS	T1	T2	L95CIN	U95CIN	L95CID	U95CID	RDIFF	RL90CI	RU90CI	
1	7.176	4.549	5975.9776095	6766.3502867	5684.6147810	6436.4523040	105.13	97.94	112.84	
2	8.357	4.593	5178.3488691	5784.4609576	4853.1779159	5421.2296012	106.70	100.17	113.66	

L95CIN = Lower 95% C.I. for Numerator Treatment Mean
 L95CID = Lower 95% C.I. for Denominator Treatment Mean
 L90CI = Lower 90% C.I. for Treatment Difference
 RL90CI = Lower 90% C.I. for Ratio of Treatment Means

U95CIN = Upper 95% C.I. for Numerator Treatment Mean
 U95CID = Upper 95% C.I. for Denominator Treatment Mean
 U90CI = Upper 90% C.I. for Treatment Difference
 RU90CI = Upper 90% C.I. for Ratio of Treatment Means

Source: CPST program \$glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis without treatment and period interaction

NAME OF FORMER VARIABLE=AUCINF

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJECT	14	101 102 103 104 105 106 108 109 110 111 112 113 114 115
SEQ	6	FLP FPL LFP LPF PFL PLF
PERIOD	3	1 2 3
TREAT	2	F L

Number of observations in by group = 28

NOTE: Due to missing values, only 26 observations can be used in this analysis.

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis withOUT treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCINF -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.63036234	0.03535749	3.46	0.0266
Error	10	0.10231075	0.01023107		
Corrected Total	25	0.63267308			

R-Square	C.V.	Root MSE	LNRESP Mean
0.838288	1.155670	0.10114878	8.75238982

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	5	0.27877780	0.05575556	5.45	0.0112
SUBJECT(SEQ)	7	0.16862173	0.02408882	2.35	0.1063
TREAT	1	0.03913597	0.03913597	3.83	0.0790
PERIOD	2	0.04382684	0.02191342	2.14	0.1682

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis withOUT treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCINF -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.29523615	0.05904723	5.77	0.0092
SUBJECT(SEQ)	7	0.15862173	0.02408882	2.35	0.1063
TREAT	1	0.03022249	0.03022249	2.95	0.1164
PERIOD	2	0.04382684	0.02191342	2.14	0.1682

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	0.29523615	0.05904723	2.45	0.1370

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
L vs F	0.07017939	1.72	0.1164	0.04083242

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis withOUT treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCLAST -----

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJECT	14	101 102 103 104 105 106 108 109 110 111 112 113 114 115
SEQ	6	FLP FPL LFP LPF PFL PLF
PERIOD	3	1 2 3
TREAT	2	F L

Number of observations in by group = 28

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis without treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCLAST -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	16	3.23345257	0.20209079	13.63	0.0001
Error	11	0.16315202	0.01483200		
Corrected Total	27	3.39660458			

R-Square	C.V.	Root MSE	LNRESP Mean
0.951966	1.415908	0.12178670	8.60131424

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	5	1.82483373	0.36496675	24.61	0.0001
SUBJECT(SEQ)	8	1.28901905	0.16112738	10.86	0.0003
TREAT	1	0.04466593	0.04466593	3.01	0.1106
PERIOD	2	0.07493386	0.03746693	2.53	0.1251

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis withOUT treatment and period interaction

----- NAME OF FORMER VARIABLE=AUCLAST -----

General Linear Models Procedure

Dependent Variable: LNRESP

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	1.61208225	0.32241645	21.74	0.0001
SUBJECT(SEQ)	8	1.28901905	0.16112738	10.86	0.0003
TREAT	1	0.03896427	0.03896427	2.63	0.1333
PERIOD	2	0.07493386	0.03746693	2.53	0.1251

Tests of Hypotheses using the Type III MS for SUBJECT(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	5	1.61208225	0.32241645	2.00	0.1828

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
L vs F	0.07502115	1.62	0.1333	0.04628607

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Medicine Co.
Analysis of Log-transformed Pharmacokinetic Parameters

16:28 Monday, March 23, 1998

Analysis without treatment and period interaction

OBS	PARAMETE	_NAME_	TREAT	LSMEAN	STDERR	NUMBER	COV1	COV2	DF
1	AUCINF	LNRESP	L	8.76771	0.029441	2	.0000332	.0008668	10
2	AUCINF	LNRESP	F	8.69753	0.029441	1	.0008668	.0000332	10
3	AUCLAST	LNRESP	L	8.61267	0.032938	2	.0000137	.0010849	11
4	AUCLAST	LNRESP	F	8.53765	0.032938	1	.0010849	.0000137	11

APPEARS THIS WAY
ON ORIGINAL

Source: CPST program\$pk3glml.sas (23MAR98) (16:28) (1)

Medicine Co.

16:28 Monday, March 23, 1998

Analysis of Log-transformed Pharmacokinetic Parameters
95% C.I.'s for least squares treatment means and
90% C.I.'s for differences between treatments
Analysis withOUT treatment and period interaction

OBS	PARAMETE	DIFF	LSMEANN1	LSMEAND1	SED	P	P1	P2	PROB	T
1	AUCINF	0.0701794	6423.4303452	5988.0924658	0.0408324	0.116	0.000	0.002	equiv	1.719
2	AUCLAST	0.0750211	5500.9182179	5103.3331277	0.0462961	0.133	0.000	0.004	equiv	1.621
OBS	T1	T2	L95CIN	U95CIN	L95CID	U95CID	RDIFF	RL90CI	RU90CI	
1	7.184	3.746	6015.5792304	6856.9334160	5607.8828180	6394.0800013	107.27	99.62	115.51	
2	6.442	3.200	5116.2321313	5914.5285952	4746.4506634	5487.0493469	107.79	99.19	117.13	

APPEARS THIS WAY
ON ORIGINAL

L95CIN = Lower 95% C.I. for Numerator Treatment Mean
L95CID = Lower 95% C.I. for Denominator Treatment Mean
L90CI = Lower 90% C.I. for Treatment Difference
RL90CI = Lower 90% C.I. for Ratio of Treatment Means

U95CIN = Upper 95% C.I. for Numerator Treatment Mean
U95CID = Upper 95% C.I. for Denominator Treatment Mean
U90CI = Upper 90% C.I. for Treatment Difference
RU90CI = Upper 90% C.I. for Ratio of Treatment Means

Source:CPST program\$pk3glm1.sas (23MAR98) (16:28) (1)

Pages 22-96 of this Amendment (dated March 25, 1998, NDA 20-873) are not included in this appendix as this information is also available in the original NDA submission as well as the archival copy of this amendment.

Copyright material

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

APPENDIX 4

CONTENTS PROCEDURE

Data Set Name: WORK.A
 Member Type: DATA
 Engine: V612
 Created: 16:48 Tuesday, May 26, 1998
 Last Modified: 16:48 Tuesday, May 26, 1998
 Protection:
 Data Set Type:
 Label:

Observations: 28
 Variables: 9
 Indexes: 0
 Observation Length: 72
 Deleted Observations: 0
 Compressed: NO
 Sorted: NO

-----Engine/Host Dependent Information-----

Data Set Page Size: 8192
 Number of Data Set Pages: 1
 File Format: 607
 First Data Page: 1
 Max Obs per Page: 113
 Obs in First Data Page: 28
 File Name: /tmp/SAS_works00000B01/a.ssd01
 Inode Number: 49
 Access Permission: rw-r--r--
 Owner Name: selena
 File Size (bytes): 16384

-----Alphabetic List of Variables and Attributes-----

#	Variable	Type	Len	Pos
4	AUCINFO	Num	8	24
6	AUCINFT	Num	8	40
3	AUCTQ	Num	8	16
5	AUCTT	Num	8	32
7	CMAX	Num	8	48
2	FORM	Char	8	8
9	PER	Num	8	64
8	SEQ	Char	8	56
1	SUBJECT	Num	8	0

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 2

OBS	SUBJECT	FORM	AUCTQ	AUCINFO	AUCTT	AUCINFT	CMAX	SEQ	PER
1	101	F	6807.40	6997.67	6827.95	7091.94	1831.40	FPL	1
2	102	F	5134.56	5469.40	5146.51	5431.35	1390.60	PFL	2
3	103	F	5505.58	5825.20	5512.79	5832.41	1396.60	LPP	3
4	104	F	6018.72	6368.39	6030.94	6380.61	1631.10	LFP	2
5	105	F	5010.23	5419.43	5020.71	5282.16	1400.90	FLP	1

6	106	F	5281.31	5633.51	5290.84	5578.35	1404.40	PLF	3
7	108	F	6344.15	6827.94	6352.38	6802.79	1644.50	FPL	1
8	109	F	3936.97	5341.58	3952.59	4545.24	1129.10	PLF	3
9	110	F	7099.79	7753.18	7114.68	7768.06	1781.30	FLP	1
10	111	F	6052.56	6305.07	6065.08	6317.59	1604.00	PFL	2
11	112	F	4974.40	5154.57	4984.64	5164.80	1291.70	LFP	2
12	113	F					710.60	LPF	3
13	114	F	5553.11	5857.37	5582.68	5861.93	1805.70	PFL	2
14	115	F	6402.11	6721.36	6409.45	6809.55	1615.96	FLP	1
15	101	L	7392.96	7634.91	7416.81	7658.77	2056.40	FPL	3
16	102	L	5787.17	6046.46	5810.77	6054.20	1851.50	PFL	3
17	103	L	4782.20	5463.71	4791.46	5472.97	1188.00	LPF	1
18	104	L	6144.08	6398.10	6155.57	6384.18	1606.70	LFP	1
19	105	L	7800.66	8056.77	7823.45	8079.56	2279.10	FLP	2
20	106	L	6448.69	6774.16	6464.65	6790.11	1691.30	PLF	2
21	108	L	5428.22	5888.30	5445.48	5906.44	1628.70	FPL	3
22	109	L	5677.34	6126.62	5686.26	6135.54	1487.00	PLF	2
23	110	L	8002.74	8393.26	8037.73	8449.27	2011.70	FLP	2
24	111	L	6036.13	6197.77	6054.44	6216.08	1575.00	PFL	3
25	112	L	4217.03	4385.42	4227.51	4395.50	1155.40	LFP	1
26	113	L					589.40	LPF	1
27	114	L	6879.24	7196.80	6906.86	7153.08	2207.90	PFL	3
28	115	L	7470.15	8244.14	7488.51	8262.50	2017.42	FLP	2

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 3

CONTENTS PROCEDURE

Data Set Name: WORK.B
 Member Type: DATA
 Engine: V612
 Created: 16:48 Tuesday, May 26, 1998
 Last Modified: 16:48 Tuesday, May 26, 1998
 Protection:
 Data Set Type:
 Label:

Observations: 28
 Variables: 16
 Indexes: 0
 Observation Length: 128
 Deleted Observations: 0
 Compressed: NO
 Sorted: YES

-----Engine/Host Dependent Information-----

Data Set Page Size: 16384
 Number of Data Set Pages: 1
 File Format: 607
 First Data Page: 1
 Max Obs per Page: 127
 Obs in First Data Page: 28
 File Name: /tmp/SAS_worka00000001/b.ssd01
 Inode Number: 51
 Access Permission: rw-r--r--
 Owner Name: selena
 File Size (bytes): 24576

-----Alphabetic List of Variables and Attributes-----

#	Variable	Type	Len	Pos
4	AUCINFO	Num	8	24
6	AUCINFT	Num	8	40
3	AUCTQ	Num	8	16
5	AUCTT	Num	8	32
7	CMAX	Num	8	48
2	FORM	Char	8	8
13	LAUCINFO	Num	8	96
14	LAUCINFT	Num	8	104
10	LAUCTQ	Num	8	72
11	LAUCTT	Num	8	80
12	L/CMAX	Num	8	88
9	PER	Num	8	64
8	SEQ	Char	8	56
16	SEQN	Num	8	120
1	SUBJECT	Num	8	0
15	TREAT	Num	8	112

-----Sort Information-----

Sortedby: TREAT SUBJECT
Validated: YES
Character Set: ASCII

16:48 Tuesday, May 26, 1998 4

Hirulog C93-310, sasrec, recalc. auc values

OBS	SUBJECT	FORM	AUCTQ	AUCINFO	AUCTT	AUCINFT	CMAX	SEQ	PER	LAUCTQ	LAUCTT	LCMAX	LAUCINFO	LAUCINFT	TREAT	SEQN
1	101	F	6807.40	6997.67	6827.95	7091.94	1831.40	FPL	1	8.82577	8.82878	7.51284	8.85333	8.86671	1	1
2	102	F	5134.56	5469.40	5146.51	5481.35	1390.60	PFL	2	8.54375	8.54607	7.23749	8.60692	8.60911	1	2
3	103	F	5505.58	5825.20	5512.79	5832.41	1396.60	LFP	3	8.61352	8.61483	7.24180	8.66995	8.67119	1	3
4	104	F	6018.72	6368.39	6030.94	6380.61	1631.10	LFP	2	8.70263	8.70466	7.39701	8.75910	8.76102	1	4
5	105	F	5010.23	5419.43	5020.71	5282.16	1400.90	FLP	1	8.51924	8.52133	7.24487	8.59775	8.57209	1	5
6	106	F	5281.31	5633.51	5290.84	5578.35	1404.40	PLF	3	8.57193	8.57373	7.24737	8.63649	8.62665	1	6
7	108	F	6344.15	6827.94	6352.38	6802.79	1644.50	PFL	1	8.75529	8.75658	7.40519	8.82878	8.82509	1	1
8	109	F	3936.97	5341.58	3952.59	4545.24	1129.10	PLF	3	8.27817	8.28213	7.02918	8.58328	8.42184	1	6
9	110	F	7099.79	7753.18	7114.68	7768.06	1781.30	FLP	1	8.86782	8.86992	7.48510	8.95586	8.95778	1	5
10	111	F	6052.56	6305.07	6065.08	6317.59	1604.00	PFL	2	8.70824	8.71030	7.38026	8.74911	8.75109	1	2
11	112	F	4974.40	5154.57	4984.64	5164.80	1291.70	LFP	2	8.51206	8.51412	7.16371	8.54764	8.54962	1	4
12	113	F					710.60	LFP	3			6.56611			1	3
13	114	F	5553.11	5857.37	5582.68	5861.93	1805.70	PFL	2	8.62211	8.62742	7.49870	8.67546	8.67623	1	2
14	115	F	6402.11	6721.36	6409.43	6809.55	1615.96	FLP	1	8.76438	8.76553	7.38768	8.81305	8.82608	1	5
15	101	L	7392.96	7634.91	7416.81	7658.77	2056.40	PFL	3	8.90828	8.91150	7.62871	8.94049	8.94361	2	1
16	102	L	5787.17	6046.46	5810.77	6054.20	1851.50	PFL	3	8.66340	8.66747	7.52375	8.70723	8.70851	2	2
17	103	L	4782.20	5463.71	4791.46	5472.97	1188.00	LFP	1	8.47266	8.47459	7.08003	8.60588	8.60758	2	3
18	104	L	6144.08	6398.10	6155.57	6384.18	1606.70	LFP	1	8.72324	8.72511	7.38194	8.76376	8.76158	2	4

19	105	L	7800.66	8056.77	7823.45	8079.56	2279.10	FLP	2	8.96196	8.96488	7.73154	8.99427	8.99709	2	5
20	106	L	6448.69	6774.16	6464.65	6790.11	1691.30	PLF	2	8.77163	8.77410	7.43325	8.82087	8.82322	2	6
21	108	L	5428.22	5888.30	5445.48	5206.44	1628.70	FPL	3	8.59937	8.60254	7.39554	8.68072	8.68380	2	1
22	109	L	5677.34	6126.62	5686.26	6135.54	1487.00	PLF	2	8.64424	8.64581	7.30452	8.72040	8.72185	2	6
23	110	L	8002.74	8393.26	8037.73	8449.27	2011.70	FLP	2	8.98754	8.99190	7.60674	9.02518	9.04184	2	5
24	111	L	6036.13	6197.77	6054.44	6216.08	1575.00	PFL	3	8.70552	8.70855	7.36201	8.73194	8.73489	2	2
25	112	L	4217.03	4385.42	4227.51	4395.90	1155.40	LFP	1	8.34689	8.34937	7.05220	8.38604	8.38843	2	4
26	113	L				589.40	LPP	1				6.37911			2	3
27	114	L	6879.24	7196.80	6906.86	7153.08	2207.90	PFL	3	8.83626	8.84027	7.69980	8.88139	8.87530	2	2
28	115	L	7470.15	8244.14	7488.51	8262.50	2017.42	FLP	2	8.91867	8.92113	7.60957	9.01726	9.01948	2	5

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 5

General Linear Models Procedure
Class Level Information

Class	Levels	Values
PER	3	1 2 3
TREAT	2	1 2
SEQN	6	1 2 3 4 5 6

Number of observations in data set = 28

Group	Obs	Dependent Variables
1	28	CNAX LCNAX
2	26	LAUCTQ LAUCTT LAUCINFQ LAUCINFY

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 6

General Linear Models Procedure

Dependent Variable: CNAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	16	3884795.63237467	242799.72702342	7.60	0.0008
Error	11	351614.68332534	31964.97121139		

Corrected Total 27 4236410.31570001

R-Square	C.V.	Root MSE	CMAX Mean
0.917002	11.38169	178.78750295	1570.83500000

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	568300.35950239	113660.07190048	3.56	0.0370
PER	2	228269.69697125	114134.84848562	3.57	0.0638
TREAT	1	189284.25150268	189284.25150268	5.92	0.0332
PER*TREAT	2	132745.16277126	66372.58138563	2.08	0.1710
SUBJECT(SEQN)	6	810579.03251009	135096.50541835	4.23	0.0189

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	568300.35950239	113660.07190048	0.84	0.5658

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 7

General Linear Models Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	16	2.36475381	0.14779711	14.83	0.0001
Error	11	0.10965427	0.00996857		
Corrected Total	27	2.47440808			

R-Square	C.V.	Root MSE	LCMAX Mean
0.955685	1.363799	0.09984273	7.32092847

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	0.42683937	0.08536787	8.56	0.0016
PER	2	0.09827970	0.04913985	4.93	0.0296
TREAT	1	0.04460744	0.04460744	4.47	0.0580
PER*TREAT	2	0.07291938	0.03645969	3.66	0.0606
SUBJECT(SEQN)	6	0.64183654	0.10697276	10.73	0.0005

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	0.42683937	0.08536787	0.80	0.5887

Hirulog C93-310, sasrec, recalc. auc values.

16:48 Tuesday, May 26, 1998 8

General Linear Models Procedure
Least Squares Means

TREAT	CMA LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN1=LSMEAN2
1	1412.33793	51.48468	0.0001	0.0332
2	1578.48231	51.46468	0.0001	

TREAT	LCMA LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN1=LSMEAN2
1	7.23028256	0.02875129	0.0001	0.0580
2	7.31093770	0.02875129	0.0001	

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 9

General Linear Models Procedure
Least Squares Means

SEQN	CMA LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN(1)=LSMEAN(j)	1/j	1	2	3	4	5	6
1	1641.44595	151.07406	0.0001	1 .	0.4822	0.0264	0.8748	0.7236	0.0569		
2	1769.44290	118.61223	0.0001	2 0.4822	.	0.0042	0.3043	0.7521	0.0175		
3	1063.25881	127.59345	0.0001	3 0.0264	0.0042	.	0.0062	0.0080	0.4763		
4	1607.26113	124.96027	0.0001	4 0.8748	0.3043	0.0062	.	0.6446	0.0613		
5	1706.32581	122.80507	0.0001	5 0.7236	0.7521	0.0080	0.6446	.	0.0069		
6	1184.72610	129.50771	0.0001	6 0.0569	0.0175	0.4763	0.0613	0.0069	.		

SEQN	LCMA LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN(1)=LSMEAN(j)	1/j	1	2	3	4	5	6
1	7.38976175	0.08436633	0.0001	1 .	0.4079	0.0022	0.9807	0.9652	0.0290		
2	7.47433105	0.06623823	0.0001	2 0.4079	.	0.0002	0.3202	0.4771	0.0071		
3	6.88975131	0.07125374	0.0001	3 0.0022	0.0002	.	0.0002	0.0008	0.0534		
4	7.38683599	0.06978326	0.0001	4 0.9807	0.3202	0.0002	.	0.9507	0.0233		
5	7.39421331	0.06857970	0.0001	5 0.9652	0.4771	0.0008	0.9507	.	0.0052		

6 7.08876737 0.07232275 0.0004 6 0.0290 0.0071 0.0534 0.0233 0.0052

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 10

General Linear Models Procedure

Dependent Variable: LAUCTQ

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.70564627	0.04704308	4.79	0.0083
Error	10	0.09821445	0.00982145		
Corrected Total	25	0.80386073			
	R-Square	C.V.	Root MSE		LAUCTQ Mean
	0.877822	1.141011	0.09910321		8.68555993

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17908329	0.04477082	4.56	0.0236
PER	2	0.07939145	0.03969572	4.04	0.0517
TREAT	1	0.02292346	0.02292346	2.33	0.1576
PER*TREAT	2	0.07620878	0.03810439	3.88	0.0566
SUBJECT(SEQN)	5	0.18872996	0.03774599	3.84	0.0334

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17908329	0.04477082	1.19	0.4182

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 11

General Linear Models Procedure

Dependent Variable: LAUCTT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.70715822	0.04714388	4.83	0.0081
Error	10	0.09765608	0.00976561		

Corrected Total 25 0.80481430

R-Square C.V.
0.878660 1.137420

Root MSE
0.09882109

LAUCTT Mean
8.68817767

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17905943	0.04476486	4.58	0.0232
PER	2	0.07962093	0.03981046	4.08	0.0507
TREAT	1	0.02325703	0.02325703	2.38	0.1538
PER*TREAT	2	0.07578440	0.03789220	3.88	0.0566
SUBJECT(SEQN)	5	0.18873639	0.03774728	3.87	0.0328

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17905943	0.04476486	1.19	0.4182

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 12

General Linear Models Procedure

Dependent Variable: LAUCINFQ

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.54042730	0.03602849	3.91	0.0175
Error	10	0.09224404	0.00922440		
Corrected Total	25	0.63267134			

R-Square C.V.
0.854199 1.097343

Root MSE
0.09604376

LAUCINFQ Mean
8.75238994

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.13722446	0.03430611	3.72	0.0419
PER	2	0.05196219	0.02598110	2.82	0.1071
TREAT	1	0.07424112	0.07424112	1.54	0.2424
PER*TREAT	2	0.03624805	0.01812402	1.96	0.1907
SUBJECT(SEQN)	5	0.14243884	0.02848777	3.09	0.0608

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.13722446	0.03430611	1.20	0.4122

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 13

General Linear Models Procedure

Dependent Variable: LAUCINFT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.63585348	0.04239023	4.50	0.0105
Error	10	0.09413334	0.00941333		
Corrected Total	25	0.72998682			

R-Square	C.V.	Root MSE	LAUCINFT Mean
0.871048	1.109209	0.09702234	8.74698726

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.15926557	0.03981639	4.23	0.0293
PER	2	0.07131062	0.03565531	3.79	0.0596
TREAT	1	0.02453320	0.02453320	2.61	0.1375
PER*TREAT	2	0.04941797	0.02470898	2.62	0.1212
SUBJECT (SEQN)	5	0.16521836	0.03304367	3.51	0.0431

Tests of Hypotheses using the Type III MS for SUBJECT (SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.15926557	0.03981639	1.20	0.4120

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 14

General Linear Models Procedure
Least Squares Means

TREAT	LAUCTQ LSMEAN	LAUCTT LSMEAN	LAUCINPQ LSMEAN	LAUCINPT LSMEAN
1	Non-est	Non-est	Non-est	Non-est

2 Non-est Non-est Non-est Non-est

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 15

General Linear Models Procedure
Least Squares Means

SEQN	LAUCTQ LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
1	8.66932154	0.08061422	0.0001	1	0.6201	.	0.6697	0.9556	0.0718		
2	8.71853321	0.06766127	0.0001	2	0.6201	.	0.9725	0.6370	0.0402		
3	Non-est	.	.	3	.	.	.	.	.	.	.
4	8.72153440	0.07496174	0.0001	4	0.6697	0.9725	.	.	0.6512	0.0415	
5	8.66370094	0.07066414	0.0001	5	0.9556	0.6370	.	0.6512	.	0.0235	
6	8.42991048	0.07513382	0.0001	6	0.0718	0.0402	.	0.0415	0.0235	.	

SEQN	LAUCTT LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
1	8.67209480	0.08038473	0.0001	1	0.6156	.	0.6741	0.9592	0.0706		
2	8.72181639	0.06746866	0.0001	2	0.6156	.	0.9853	0.6358	0.0392		
3	Non-est	.	.	3	.	.	.	.	.	.	.
4	8.72341874	0.07474834	0.0001	4	0.6741	0.9853	.	.	0.6579	0.0412	
5	8.66695581	0.07046298	0.0001	5	0.9592	0.6358	.	0.6579	.	0.0227	
6	8.43211491	0.07491994	0.0001	6	0.0706	0.0392	.	0.0412	0.0227	.	

SEQN	LAUCINFQ LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
1	8.76457127	0.07812555	0.0001	1	0.8962	.	0.7404	0.8989	0.1440		
2	8.75209218	0.06557247	0.0001	2	0.8962	.	0.7522	0.8242	0.1822		
3	Non-est	.	.	3	.	.	.	.	.	.	.
4	8.72534349	0.07264757	0.0001	4	0.7404	0.7522	.	.	0.6767	0.2628	
5	8.77699165	0.06848264	0.0001	5	0.8989	0.8242	.	0.6767	.	0.0444	
6	8.58188202	0.07281434	0.0001	6	0.1440	0.1822	.	0.2628	0.0444	.	

SEQN	LAUCINFQ LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
1	8.75298788	0.07892156	0.0001	1	0.9864	.	0.8786	0.9452	0.0950		
2	8.75133746	0.06624058	0.0001	2	0.9864	.	0.8461	0.9638	0.1061		
3	Non-est	.	.	3	.	.	.	.	.	.	.
4	8.73476034	0.07338777	0.0001	4	0.8786	0.8461	.	.	0.9268	0.1388	
5	8.74620062	0.06918041	0.0001	5	0.9452	0.9638	.	0.9268	.	0.0358	
6	8.53829945	0.07355624	0.0001	6	0.0950	0.1061	.	0.1388	0.0358	.	

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 16

TREAT=1

Variable	Mean	CV
SUBJECT	108.0714286	4.2861161
AUCTQ	5701.61	15.1760053
AUCINFQ	6128.82	12.6736132
AUCTT	5714.71	15.1473214
AUCINF	6070.52	14.7511250
CNAX	1474.13	20.4472468
PER	1.9285714	42.9718038
LAUCTQ	8.6372998	1.8319730
LAUCTT	8.6396459	1.8269798
LCNAX	7.2712359	3.3809944
LAUCINFQ	8.7135927	1.4185253
LAUCINF	8.7011149	1.7030078
SEQN	3.5000000	49.8033811

TREAT=2

Variable	Mean	CV
SUBJECT	108.0714286	4.2861161
AUCTQ	6312.82	18.4154040
AUCINFQ	6677.42	17.7491041
AUCTT	6331.50	18.4533729
AUCINF	6689.12	17.8194950
CNAX	1667.54	27.7987450
PER	2.0714286	40.0082311
LAUCTQ	8.7338201	2.1995568
LAUCTT	8.7367095	2.2031525
LCNAX	7.3706210	4.7887873
LAUCINFQ	8.7911872	2.1030950
LAUCINF	8.7928596	2.1067589
SEQN	3.5000000	49.8033811

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 17

OBS SUBJECT FORM AUCTQ AUCINFQ AUCTT AUCINF CNAX SEQ PER LAUCTQ LAUCTT LCNAX LAUCINFQ LAUCINF TREAT SEQN

1	101	F	6807.40	6997.67	6827.95	7091.94	1831.40	FPL	1	8.82577	8.82878	7.51284	8.85333	8.86671	1	1
2	102	F	5134.56	5469.40	5146.51	5481.35	1390.60	PFL	2	8.54375	8.54607	7.23749	8.60692	8.60911	1	2
3	103	F	5505.58	5825.20	5512.79	5832.41	1396.60	LFP	3	8.61352	8.61483	7.24180	8.66995	8.67110	1	3
4	104	F	6018.72	6368.39	6030.94	6380.61	1631.10	LFP	2	8.70263	8.70466	7.39701	8.75910	8.76102	1	4
5	105	F	5019.23	5419.43	5020.71	5282.16	1400.90	FLP	1	8.51924	8.52133	7.24487	8.59775	8.57209	1	5
6	106	F	5281.31	5633.51	5290.84	5578.35	1404.40	PLF	3	8.57193	8.57373	7.24737	8.63649	8.62665	1	6
7	108	F	6344.15	6827.94	6352.38	6802.79	1644.50	FPL	1	8.75529	8.75658	7.40519	8.82878	8.82509	1	1
8	109	F	3936.97	5341.58	3952.59	4545.24	1129.10	PLF	3	8.27817	8.28213	7.02918	8.58328	8.42184	1	6
9	110	F	7099.79	7753.18	7114.68	7768.06	1781.30	FLP	1	8.86782	8.86992	7.48510	8.95586	8.95778	1	5
10	111	F	6052.56	6305.07	6065.08	6317.59	1604.00	PFL	2	8.70824	8.71030	7.38026	8.74911	8.75109	1	2
11	112	F	4974.40	5154.57	4984.64	5164.80	1291.70	LFP	2	8.51206	8.51412	7.16371	8.54764	8.54962	1	4
12	113	F					710.60	LFP	3			6.56611			1	3
13	114	F	5553.11	5857.37	5582.60	5861.93	1805.70	PFL	2	8.62211	8.62742	7.49870	8.67546	8.67623	1	2
14	115	F	6402.11	6721.36	6409.45	6809.55	1615.96	FLP	1	8.76438	8.76553	7.38768	8.81305	8.82608	1	5
15	101	L	7392.96	7634.91	7416.81	7658.77	2056.40	FPL	3	8.90828	8.91150	7.62871	8.94049	8.94361	2	1
16	102	L	5787.17	6046.46	5810.77	6054.20	1851.50	PFL	3	8.66340	8.66747	7.52375	8.70723	8.70851	2	2
17	103	L	4782.20	5463.71	4791.46	5472.97	1188.00	LFP	1	8.47266	8.47459	7.08003	8.60588	8.60758	2	3
18	104	L	6144.08	6398.10	6155.57	6384.18	1606.70	LFP	1	8.72324	8.72511	7.38194	8.76376	8.76158	2	4
19	105	L	7800.66	8056.77	7823.45	8079.56	2279.10	FLP	2	8.96196	8.96488	7.73154	8.99427	8.99709	2	5
20	106	L	6448.69	6774.16	6464.65	6790.11	1691.30	PLF	2	8.77163	8.77410	7.43325	8.82087	8.82322	2	6
21	108	L	5428.22	5888.30	5445.48	5906.44	1628.70	FPL	3	8.59937	8.60254	7.39554	8.68072	8.68380	2	1
22	109	L	5677.34	6126.62	5686.26	6135.54	1487.00	PLF	2	8.64424	8.64581	7.30452	8.72040	8.72185	2	6
23	110	L	8002.74	8393.26	8037.73	8449.27	2011.70	FLP	2	8.98754	8.99190	7.60674	9.03518	9.04184	2	5
24	111	L	6036.13	6197.77	6054.44	6216.08	1575.00	PFL	3	8.70552	8.70855	7.36201	8.73194	8.73489	2	2
25	112	L	4217.03	4385.42	4227.51	4395.90	1155.40	LFP	1	8.34689	8.34937	7.05220	8.38604	8.38843	2	4
26	113	L					589.40	LFP	1			6.37911			2	3
27	114	L	6879.24	7196.80	6906.86	7153.08	2207.90	PFL	3	8.83626	8.84027	7.69980	8.88139	8.87530	2	2
28	115	L	7470.15	8244.14	7488.51	8262.50	2017.42	FLP	2	8.91867	8.92113	7.60957	9.01726	9.01948	2	5

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 18

General Linear Models Procedure
Class Level Information

Class	Levels	Values
PER	3	1 2 3
TREAT	2	1 2
SEON	6	1 2 3 4 5 6

Number of observations in data set = 28

Group	Obs	Dependent Variables
1	28	CNAX LCNAX

NOTP: Variables in each group are consistent with respect to the presence or absence of missing values.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 19

General Linear Models Procedure

Dependent Variable: CMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	14	3752050.46960342	268003.60497167	7.19	0.0005
Error	13	484359.84609659	37258.44969974		
Corrected Total	27	4236410.31570001			
	R-Square	C.V.	Root MSE		CMAX Mean
	0.885667	12.28802	193.02447953		1570.83500000

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	573035.79101924	114607.15820385	3.08	0.0476
PER	2	236297.81703143	118148.90851571	3.17	0.0756
TRFAT	1	222394.37451077	222394.37451077	5.97	0.0296
SUBJECT(SEQN)	6	810579.03251008	135096.50541835	3.63	0.0245

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	573035.79101924	114607.15820385	0.85	0.5622

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 20

General Linear Models Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	14	2.29183443	0.16370246	11.66	0.0001
Error	13	0.18257365	0.01404413		

Corrected Total 27 2.47440808

R-Square	C.V.	Root MSE	LCMAX Mean
0.926215	1.618755	0.11850792	7.32092847

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	0.42585206	0.08517041	6.06	0.0041
PER	2	0.09963138	0.04981569	3.55	0.0590
TREAT	1	0.05617003	0.05617003	4.00	0.0669
SUBJECT (SEQN)	6	0.64183654	0.10697276	7.62	0.0012

Tests of Hypotheses using the Type III MS for SUBJECT (SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	5	0.42585206	0.08517041	0.80	0.5897

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 21

General Linear Models Procedure
Least Squares Means

TREAT	CMAX LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN1=LSMEAN2
1	1405.79478	55.46795	0.0001	0.0296
2	1585.02545	55.46795	0.0001	

TREAT	LCMAX LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN1=LSMEAN2
1	7.22557279	0.03405470	0.0001	0.0669
2	7.31564747	0.03405470	0.0001	

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 22

General Linear Models Procedure
Least Squares Means

SEQN	CMAX LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
				i/j						

1	1682.84529	140.85900	0.0001	1	0.8138	0.0016	0.1950	0.2682	0.0572
2	1642.60788	85.71545	0.0001	2	0.8138	0.0005	0.1666	0.0904	0.0237
3	1015.94424	100.71980	0.0001	3	0.0016	0.0005	0.0117	0.0001	0.0739
4	1442.61176	101.23756	0.0001	4	0.1352	0.1666	0.0117	0.0051	0.3896
5	1280.47550	92.34170	0.0001	5	0.2682	0.0904	0.0001	0.0051	0.0017
6	1307.97514	107.69333	0.0001	6	0.0572	0.0237	0.0739	0.3896	0.0017

SEQN	LCMAX LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)	1	2	3	4	5	6
1	7.43025553	0.08648078	0.0001	1	0.6956	0.0001	0.1452	0.3796	0.0359		
2	7.38914558	0.05262524	0.0001	2	0.6956	0.0001	0.1561	0.1110	0.0180		
3	6.84347271	0.06183721	0.0001	3	0.0001	0.0001	0.0004	0.0001	0.0035		
4	7.26297410	0.06215508	0.0001	4	0.1452	0.1561	0.0004	0.0059	0.3459		
5	7.52567739	0.05669344	0.0001	5	0.3796	0.1110	0.0001	0.0059	0.0016		
6	7.17213548	0.06611862	0.0001	6	0.0359	0.0180	0.0035	0.3459	0.0016		

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 23

General Linear Models Procedure

Dependent Variable: LAUCTQ

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	0.62943749	0.04841827	3.33	0.0225
Error	12	0.17442324	0.01453527		
Corrected Total	25	0.80386073			

R-Square	C.V.	Root MSE	LAUCTQ Mean
0.783018	1.388078	0.12056231	8.68555993

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17590686	0.04397672	3.03	0.0611
PER	2	0.06345242	0.03172621	2.18	0.1554
TREAT	1	0.05076866	0.05076866	3.49	0.0862
SUBJECT(SEQN)	5	0.18872996	0.03774599	2.60	0.0815

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17590685	0.04397672	1.17	0.4252

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 24

General Linear Models Procedure

Dependent Variable: LAUCTT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	0.63137382	0.04856722	3.36	0.0218
Error	12	0.17344048	0.01445337		
Corrected Total	25	0.80481430			
R-Square		C.V.	Root MSE	LAUCTT Mean	
0.784496		1.383745	0.12022218	8.68817767	

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17594733	0.04398683	3.04	0.0602
PER	2	0.06370993	0.03185497	2.20	0.1530
TREAT	1	0.05124388	0.05124388	3.55	0.0842
SUBJECT(SEQN)	5	0.18873639	0.03774728	2.61	0.0803

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.17594733	0.04398683	1.17	0.4251

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 25

General Linear Models Procedure

Dependent Variable: LAUCINFO

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	0.50417925	0.03878302	3.62	0.0164
Error	12	0.12849208	0.01070767		
Corrected Total	25	0.63267134			

R-Square	C.V.	Root MSE	LAUCINFQ Mean
0.796905	1.182282	0.10347789	8.75238994

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.13406481	0.03351620	3.13	0.0558
PER	2	0.04382684	0.02191342	2.05	0.1719
TRFAT	1	0.03022247	0.03022247	2.82	0.1188
SUBJECT(SEQN)	5	0.14243884	0.02848777	2.66	0.0766

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.13406481	0.03351620	1.18	0.4213

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 26

General Linear Models Procedure

Dependent Variable: LAUCINFQ

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	0.58643551	0.04511042	3.77	0.0140
Error	12	0.14355131	0.01196261		
Corrected Total	25	0.72998682			

R-Square	C.V.	Root MSE	LAUCINFQ Mean
0.803351	1.250416	0.10937371	8.74698726

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.15514483	0.03878621	3.24	0.0507
PER	2	0.05993234	0.02996617	2.50	0.1233
TREAT	1	0.04708177	0.04708177	3.94	0.0706
SUBJECT(SEQN)	5	0.16521836	0.03304367	2.76	0.0693

Tests of Hypotheses using the Type III MS for SUBJECT(SEQN) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQN	4	0.15514483	0.03878621	1.17	0.4222

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 27

General Linear Models Procedure
Least Squares Means

TREAT	LAUCTQ LSMEAN	LAUCTT LSMEAN	LAUCINFQ LSMEAN	LAUCINFT LSMEAN
1	Non-est	Non-est	Non-est	Non-est
2	Non-est	Non-est	Non-est	Non-est

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 28

General Linear Models Procedure
Least Squares Means

SEQN	LAUCTQ LSMEAN	Std Err LSMEAN	Pr > T H0:LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)					
					1	2	3	4	5	6
1	8.72219865	0.08354527	0.0001	1	.	0.4264	.	0.1871	0.4487	0.0909
2	8.63858174	0.05488674	0.0001	2	0.4264	.	.	0.4666	0.0745	0.1796
3	Non-est	.	.	3	.	.	.	.	.	.
4	8.57287938	0.06392178	0.0001	4	0.1871	0.4666	.	.	0.0163	0.6230
5	8.80408339	0.06022696	0.0001	5	0.4487	0.0745	.	0.0163	.	0.0099
6	8.52568839	0.06422009	0.0001	6	0.0909	0.1796	.	0.6230	0.0099	.

SEQN	LAUCTT LSMEAN	Std Err LSMEAN	Pr > T H0:LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)					
					1	2	3	4	5	6
1	8.72450676	0.08330958	0.0001	1	.	0.4297	.	0.1858	0.4445	0.0900
2	8.64173920	0.05473190	0.0001	2	0.4297	.	.	0.4596	0.0742	0.1754
3	Non-est	.	.	3	.	.	.	.	.	.
4	8.57515169	0.06374145	0.0001	4	0.1858	0.4596	.	.	0.0158	0.6221
5	8.80693238	0.06005706	0.0001	5	0.4445	0.0742	.	0.0158	.	0.0097
6	8.52797000	0.06403891	0.0001	6	0.0900	0.1754	.	0.6221	0.0097	.

SEQN	LAUCINFQ LSMEAN	Std Err LSMEAN	Pr > T H0:LSMEAN=0	Pr > T 1/j	H0: LSMEAN(1)=LSMEAN(j)					
					1	2	3	4	5	6
1	8.78998031	0.07170639	0.0001	1	.	0.2553	.	0.0933	0.3771	0.1783
2	8.68583190	0.04710895	0.0001	2	0.2553	.	.	0.4187	0.0248	0.6978
3	Non-est	.	.	3	.	.	.	.	.	.
4	8.62302395	0.05486367	0.0001	4	0.0933	0.4187	.	.	0.0043	0.6639

5	8.87229084	0.05169243	0.0001	5	0.3771	0.0248	0.0043	0.0182
6	8.65879252	0.05511971	0.0001	6	0.1783	0.6978	0.6639	0.0182

SEQN	LAUCINF LSMEAN	Std Err LSMEAN	Pr > T H0: LSMEAN=0	Pr > T 1/j	H0: LSMEAN(i)-LSMEAN(j)	1	2	3	4	5	6
1	8.79694235	0.07579198	0.0001	1	0.2620		0.0849	0.5236	0.0834		
2	8.68852563	0.04979306	0.0001	2	0.2620		0.3732	0.0463	0.3194		
3	Non-est			3							
4	8.61519188	0.05798962	0.0001	4	0.0849	0.3732		0.0069	0.9879		
5	8.85929184	0.05463770	0.0001	5	0.5236	0.0463		0.0069		0.0117	
6	8.61387344	0.05826024	0.0001	6	0.0834	0.3194		0.9879	0.0117		

NOTE: To ensure overall protection level, only probabilities associated with pre-planned comparisons should be used.

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 29

TREAT=1

Variable	Mean	CV
SUBJECT	108.0714286	4.2861161
AUCTQ	5701.61	15.1760053
AUCINFO	6128.82	12.6736132
AUCTT	5714.71	15.1473214
AUCINFT	6070.52	14.7511250
CMAK	1474.13	20.4472468
PER	1.9285714	42.9718038
LAUCTQ	8.6372998	1.8319730
LAUCTT	8.6396459	1.8269798
LCMAK	7.2712359	3.3809944
LAUCINFO	8.7135927	1.4185253
LAUCINFT	8.7011149	1.7030078
SEQN	3.5000000	49.8033811

APPEARS THIS WAY
ON ORIGINAL

TREAT=2

Variable	Mean	CV
SUBJECT	108.0714286	4.2861161
AUCTQ	6312.82	18.4154040
AUCINFO	6677.42	17.7491041
AUCTT	6331.50	18.4533729
AUCINFT	6689.12	17.8194950

APPEARS THIS WAY
ON ORIGINAL

CMAx	1667.54	27.7987450
PER	2.0714286	40.0082311
LAUCTQ	8.7338201	2.1995568
LAUCTT	8.7367095	2.2031525
LCMAx	7.3706210	4.7887873
LAUCINFQ	8.7911872	2.1030950
LAUCINFT	8.7928596	2.1067589
SEQN	3.5000000	49.8033811

Hirulog C93-310, sasrec, recalc. auc values

16:48 Tuesday, May 26, 1998 30

OBS	SUBJECT	FORM	AUCTQ	AUCINFQ	AUCTT	AUCINFT	CMAx	SEQ	PER	LAUCTQ	LAUCTT	LCMAx	LAUCINFQ	LAUCINFT	TREAT	SEQN
1	101	F	6807.40	6997.67	6827.95	7091.94	1831.40	FPL	1	8.82577	8.82878	7.51284	8.85333	8.86671	1	1
2	102	F	5134.56	5469.40	5146.51	5481.35	1390.60	PFL	2	8.54375	8.54607	7.23749	8.60692	8.60911	1	2
3	103	F	5505.58	5825.20	5512.79	5832.41	1396.60	LFP	3	8.61352	8.61483	7.24180	8.66995	8.67119	1	3
4	104	F	6018.72	6368.39	6030.94	6380.61	1631.10	LFP	2	8.70263	8.70466	7.39701	8.75910	8.76102	1	4
5	105	F	5010.23	5413.43	5020.71	5282.16	1400.90	FLP	1	8.51924	8.52133	7.24487	8.59775	8.57209	1	5
6	106	F	5281.31	5633.51	5290.84	5578.35	1404.40	PLF	3	8.57192	8.57373	7.24737	8.63649	8.62665	1	6
7	108	F	6344.15	6827.94	6352.38	6802.79	1644.50	FPL	1	8.75529	8.75658	7.40519	8.82878	8.82509	1	1
8	109	F	3936.97	5341.58	3952.59	4545.24	1129.10	PLF	3	8.27817	8.28213	7.02918	8.58328	8.42184	1	6
9	110	F	7099.79	7753.18	7114.68	7768.06	1781.30	FLP	1	8.86782	8.86992	7.48510	8.95586	8.95778	1	5
10	111	F	6052.56	6305.07	6065.08	6317.59	1604.00	PFL	2	8.70824	8.71030	7.38026	8.74911	8.75109	1	2
11	112	F	4974.40	5154.57	4984.64	5164.80	1291.70	LFP	2	8.51206	8.51412	7.16371	8.54764	8.54962	1	4
12	113	F					710.60	LFP	3			6.56611			1	3
13	114	F	5553.11	5857.37	5582.68	5861.93	1805.70	PFL	2	8.62211	8.62742	7.49870	8.67546	8.67623	1	2
14	115	F	6402.11	6721.36	6409.45	6809.55	1615.96	FLP	1	8.76438	8.76553	7.38768	8.81305	8.82608	1	5
15	101	L	7392.96	7634.91	7416.81	7658.77	2056.40	FPL	3	8.90828	8.91150	7.62871	8.94049	8.94361	2	1
16	102	L	5787.17	6046.46	5810.77	6054.20	1851.50	PFL	3	8.66340	8.66747	7.52375	8.70723	8.70851	2	2
17	103	L	4782.20	5463.71	4791.46	5472.97	1188.00	LFP	1	8.47266	8.47459	7.08003	8.60588	8.60758	2	3
18	104	L	6144.08	6398.10	6155.57	6384.18	1606.70	LFP	1	8.72324	8.72511	7.38194	8.76376	8.76158	2	4
19	105	L	7800.66	8056.77	7823.45	8079.56	2279.10	FLP	2	8.96196	8.96488	7.73154	8.99427	8.99709	2	5
20	106	L	6448.69	6774.16	6464.65	6790.11	1691.30	PLF	2	8.77163	8.77410	7.43325	8.82087	8.82322	2	6
21	108	L	5428.22	5888.30	5445.48	5906.44	1628.70	FPL	3	8.59937	8.60254	7.39554	8.68072	8.68380	2	1
22	109	L	5677.34	6126.62	5686.26	6135.54	1487.00	PLF	2	8.64424	8.64581	7.30452	8.72040	8.72185	2	6
23	110	L	8002.74	8393.26	8037.73	8449.27	2011.70	FLP	2	8.98754	8.99190	7.60674	9.03518	9.04184	2	5
24	111	L	6036.13	6197.77	6054.44	6216.08	1575.00	PFL	3	8.70552	8.70855	7.36201	8.73194	8.73489	2	2
25	112	L	4217.03	4385.42	4227.51	4395.90	1155.40	LFP	1	8.34689	8.34937	7.05220	8.38604	8.38843	2	4
26	113	L					589.40	LFP	1			6.37911			2	3
27	114	L	6879.24	7196.80	6906.86	7153.08	2207.90	PFL	3	8.83626	8.84027	7.69980	8.88139	8.87530	2	2
28	115	L	7470.15	8244.14	7488.51	8262.50	2017.42	FLP	2	8.91867	8.92113	7.60957	9.01726	9.01948	2	5

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-873

Submission Date: December 29, 1997

Bivalirudin Injection

BRAND NAME: HIRULOG®

APR 30 1998

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

REVIEWER: Arzu Selen, Ph.D.

TYPE OF SUBMISSION: Amendment to NDA

Code: 1S

The objective of this review is to request critical assay related information from the Sponsor in order to determine whether certain studies are suitable for further assessment.

As review of the Hirulog NDA 20-873 is progressing, several issues were communicated to the Sponsor for resolution (FDA letters February 11, 1998 and March 17, 1998). The interaction with the Sponsor on some of these issues is continuing while some has been brought to a closure. An update on progress of the issues raised to date are provided in another review document that is in preparation.

COMMENTS TO BE COMMUNICATED TO THE SPONSOR:

1. Based on information in the Bioanalytical Validation Report, Appendix 2 of Section 6 of the Hirulog NDA, the assay used for analysis of bivalirudin is considered to be non-specific and the accuracy of the pharmacokinetic parameters determined by this analytical method is questionable. The enzyme conjugated monoclonal antibody, DE3, is indicated to be specific for bivalirudin, its analog H133 and PPAC((D-F)PR). Furthermore, based on information in this validation report, it is likely that DE3 would also cross-react with fragments of bivalirudin that are formed in vivo and/or ex vivo by cleavage of its amino acids. Please provide information and the supporting data on binding affinity of the bivalirudin analog H133 and bivalirudin fragments to the antibody, particularly, those that are expected to be metabolites of bivalirudin and/or its breakdown-products.
2. Please provide a list of all the bivalirudin breakdown products, and information on the conditions they were formed and the method(s) used to confirm these products/fragments.
3. Please indicate the amino acid sequence of PPAC((D-F)PR) that is recognized by the antibody and please provide background information on PPAC((D-F)PR) and the analog of BG8967, H133.
4. Please provide the batch numbers of the enzyme antibody conjugates used in the analyses of all bivalirudin studies as well as their stability and activity at the time(s) of their preparation and use, and their respective expiration date(s).

5. Please provide a copy of the SOP#160a.38 (page 26, volume 39 of the Hirulog NDA).
6. During review of the individual study reports, it appears that except Study C90-010, there were no quality controls assayed during analysis of samples in Studies: C92-305, C92-306, C93-310, C93-313, C93-316, C93-317, and C90-041. Please verify whether this information is correct and provide the values of all of the quality control samples that were assayed in C90-010.
7. Please provide a copy of the SOP utilized for acceptance criteria of the quality control samples. The acceptance range for quality control samples (mean $\pm$ 3SD) indicated in the validation report is considered to be too large to be a robust indicator of the assay performance.
8. Please provide values of all of the quality control samples assayed in all of the bivalirudin studies.
9. In individual reports (C92-305, C92-306, C93-310, C93-313, C93-316, C93-317, C90-310, C90-041), the BG8967 standards were prepared in pH 8.0 Tris buffer and stored frozen. Please provide storage conditions for each study, and the supporting stability data in the buffer.
10. Please clarify the following discrepancies noted between the individual study reports and the validation report in Appendix 2 of Section 6 of the Hirulog NDA, and provide reason(s) for the deviations from the validated assay method and if applicable, provide the data supporting the alternate approach:
 - Although BG8967 (200 μ g/ml) was used to coat the microtiter wells in the Validation Report and in some studies (C93-313 and C92-305), in Study C90-310, the concentration of BG8967 used to coat the microtiter plates was 50 μ g/ml.
 - In some of the study reports (C92-306, C93-310, C93-316, and C93-317), it is indicated that the analog H133 is used for coating the microtiter plates. The concentration of the analog H133 used in these studies, except in Study C93-317, was 1 μ g/ml. Please provide the concentration of the H133 solution used in Study C93-317 and the reason for using H133 to coat the microtiter plates.
11. Please provide clarification for the discrepancy noted within individual reports (C92-306, C93-310, C93-316, C93-317): the microtiter plates are indicated to be coated with H133-BSA in one paragraph but in a subsequent paragraph, the wells are indicated to be coated with BG8967
12. There appears to be two assay methods used in Study C90-010, it seems that in one group the samples are incubated with the antibody while in the other group the samples are incubated with enzyme coupled antibody. Please clarify the reason for different approaches.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has been reviewing the Hirulog NDA 20-873. The progress of items raised in earlier documents is addressed in another review, however, the queries raised in this document under the section of Comments to be Communicated to the Sponsor (pages 1 and 2) need to be communicated to the Sponsor as soon as possible for timely review of the Hirulog NDA 20873.

/S/

4/29/98

Arzu Selen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by /S/ 4/29/98
John Hunt, B.Sc.
Deputy Director and Acting Team Leader

FT initialed by /S/ 4/30/98
Mei-Ling Chen, Ph.D.
Director, DPE II

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

Subaru

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-873

Bivalirudin Injection

Submission Date:

February 25, 1998

BRAND NAME: HIRULOG®

MAR 12 1998

SPONSOR: Medicines Company
— **Cambridge, MA**

REVIEWER: Arzu Selen, Ph.D.

(Regulatory Liaison: Quintiles Inc.)

TYPE OF SUBMISSION: Amendment to NDA

Code: 1S

During 45-Day review of the Hirulog (bivalirudin) NDA submission, several items were noted and requested from the Sponsor. In Sponsor's February 25, 1998 letter (received March 3, 1998), some of these items were addressed while others (Items D1, D2, D3, D6, D8 and D10) were acknowledged by the Sponsor as outstanding and feedback was requested for Item D8.

The objectives of this response are to provide feedback to the Sponsor and establish timelines for resolution of the remaining items (Items D1, D2, D3, D5, D6, D7, D8 and D10).

The following list is a review of the status of the items (as listed in the FDA letter dated February 11, 1998) and the Sponsor's responses to this letter. The follow-up comments/questions are listed at the end of this section as comments to be communicated to the Sponsor.

1. Items D1, D2 and D3 which are related to analytical methods applied to measure bivalirudin and aPTT are still pending. The Sponsor should provide responses to these items by March 23.
2. Item D4: As requested, Sponsor has provided recalculated clearance values for the Study C93-310.
3. Item D5: The Sponsor states that there were no factors identified that could account for the period and period and treatment interaction observed in the study. The Sponsor is requested to perform bioequivalence testing for each period separately (Comments to be Communicated to the Sponsor).
4. Item D6 that is a list of bridging studies with additional "linking" information is still pending and the Sponsor should provide response to this item by March 23.
5. Item D7: As requested, the Sponsor has provided the report number and the location of the study report in the NDA submission. Review of this study report has led to additional questions which are also listed at the end of this section (Comments to be Communicated to the Sponsor).

6. Item D8: In response, the Sponsor has proposed to perform testing of potential drug-drug interactions for bivalirudin using mitochondria. The Sponsor has also indicated that they are going ahead with this study and are requesting FDA's view on this approach. The response to the Sponsor is under the Section, Comments to be Communicated to the Sponsor.
7. Item D9: The Sponsor provides the duration of infusion (4 h) which was incorrectly stated in Panel 3.6.3.B. Volume 1.002, page 50 and refers to the other sections in the NDA where the information was accurate.
8. Item D10 is still pending. The Sponsor was requested to comment on why the dose-adjustment recommended in patients with renal impairment in the NDA was not also included in the package insert.

COMMENTS TO BE COMMUNICATED TO THE SPONSOR:

1. The Sponsor needs to provide responses to Items D1, D2, D3, D5, D6, D7, D8 and D10 by March 23.
2. The Sponsor's response to Items D4 and D9 are accepted.
3. The bioequivalence assessment for C93-310 needs to be repeated with the recalculated AUC values [AUC(0-tlast) and AUC(0-inf)]. Furthermore, since the Sponsor has indicated that there are no known contributing factors for the observed period and period and treatment interaction effects (Item D5), these effects need to be further investigated. The Sponsor is requested to submit an ASCII file of the bivalirudin parameters [Cmax, AUC values reported in the study report (AUC(0-28) and AUC(0-inf)) and the recalculated AUC values (AUC(0-tlast), and AUC(0-inf))] for each subject with their formulation, period and sequence information on a diskette to the Agency by March 16.
4. Item D7: The Sponsor has indicated that the study report used for assessment of potential drug-drug interactions is Study Report P8967-94-06 in Volume 1.034, page 245. In Volume 1.034, on page 245, there are two Biogen study numbers (P8967-94-02 and P8967-94-06). It appears that the Study Number P8967-94-02 is for the 28-day toxicology study and the Study Number P8967-94-06 refers to the in vitro study conducted for assessment of potential drug-drug interactions with bivalirudin. It is possible that dosing information (preparation of dosing solution, verification of concentration of bivalirudin in dose solution, and stability in dosing vehicle) are included in the Study Report P8967-94-02, however, as this information is a critical component of the Study P8967-94-06, it needs to be included in the Study Report. The Sponsor is requested to provide the dosing information (preparation of dosing solution, verification of concentration of bivalirudin in dose solution, conditions of storage of bivalirudin and the dosing vehicle and stability of bivalirudin in the dosing vehicle) and copies of the supporting documentation.

Furthermore, the Sponsor is requested to verify whether the NOAEL dose in the rat, indicated to be 25 mg/kg/day, on page 123 of Volume 1.002 is accurate. Based on information presented on Panel 3.5.6B, page 124 of Volume 1.002, that is the status of rats after 28 days of iv infusion of bivalirudin, is the conclusion of lack of potential drug-drug interactions with bivalirudin, derived from the results of Study P8967-94-02, reliable?

5. Item D8: The Sponsor is encouraged to submit the proposed study protocol with detailed information on reasons for choosing to use "mitochondria" for assessment of potential drug-drug interactions instead of microsomal preparations as used in preclinical studies.
6. The Sponsor is also requested to provide ASCII files of pharmacokinetic/pharmacodynamic parameters for each study on a diskette. These files will also include the appropriate formulation, sequence, period and demographic information for each subject.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the responses from (), dated February 25, 1998, for the Medicines Company for the Hirulog NDA 20873. The outstanding items as well as the related follow-up comments are listed under the section, Comments to be Communicated to the Sponsor (pages 2 and 3 of this document). For timely completion of the clinical pharmacology and biopharmaceutics review of the NDA 20873, the Sponsor is requested to provide the information required in Item 3 on a diskette by March 16, 1998, and the responses to all of the remaining items listed above by March 23, 1998. For items that can not be completed by that date, such as the in vitro study, the Sponsor is requested to provide the date when the outstanding items will be submitted to the Agency.

/S/

Arzu Selen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by
John Hunt, B.Sc.

/S/

3/12/98

Deputy Director and Acting Team Leader

FT initialed by
Mei-Ling Chen, Ph.D.
Director, DPE II

/S/

3/12/98

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