CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-271			
Submission(s):	Type: 1S	Suppl.: 000	Letter Date: 6/28/00	Date Received: 6/28/00
Reviewer:	Sandip K. Roy, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Desirudin			
Other Name(s):	RPR205511, CGP39393			
Trade Name:	[redacted]			
Molecular Weight:	6963.52			
Molecular Formula:	$C_{287}H_{440}N_{80}O_{110}S_6$			
Relevant IND(s)/NDA(s):	IND 34,046			
Drug Class:	Anticoagulant			
Dosage Form:	Single dose (15 mg) lyophilized powder			
Route of Administration:	Subcutaneous injection			
Dosing Regimen:	15 mg every 12 hrs administered by subcutaneous injection			
Sponsor:	Aventis Pharmaceuticals Products Inc., Collegeville, PA			
Proposed Indication:	Prevention of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery			

OVERVIEW

Desirudin is a potent inhibitor of human thrombin. Desirudin, which is expressed in yeast by recombinant DNA technology using a chemically synthesized gene, differs from the natural hirudin by lack of a sulfate group on Tyr-63. It is a single polypeptide chain of 65 amino acids with 3 disulphide bridges. Desirudin is indicated for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery. Desirudin is supplied as a sterile, white, freeze dried powder for injection. The proposed dosage regimen for Desirudin is 15 mg every 12 hrs administered by SC injection with the initial dose given up to 5 to 15 minutes prior to surgery, but after induction of regional block anesthesia, if used.

A total of 21 studies were submitted under the "Human Pharmacokinetics and Bioavailability" section that were conducted with desirudin in healthy volunteers or patients using both the SC and IV route to investigate pharmacokinetics, pharmacodynamics, as well as pharmacokinetic-pharmacodynamic relationship. A [redacted] ELISA assay method was developed to measure desirudin in plasma and urine in these studies. However this method does not discriminate between native desirudin and its metabolites. [redacted], another method often used was inaccurate at plasma concentrations higher than 70 nmol/L. Concentrations higher than 70 nmol/L are reached when desirudin is given IV and only at higher SC doses (0.75 mg/kg). C_{max} achieved with the recommended SC dose of 15 mg (~0.2 mg/kg) is about [redacted] Pharmacodynamic endpoint, "aPTT prolongation", measured in plasma samples is probably a more reliable estimate of desirudin exposure in these trials for the purpose of PK guided dose adjustment. aPTT (activated partial thromboplastin time) prolongation values in healthy volunteers were dose dependent and were quite comparable to those observed in patients undergoing elective hip replacement. Repeated SC twice daily injections of desirudin led to aPTT prolongations without any accumulation effect. A fixed SC dose of 40 mg given twice daily for 10 consecutive days produced excessive bleeding in these patients, whereas, fixed doses of 15 and 20 mg had less bleeding complications and were equally effective. Thus, 15 mg bid is the recommended dose.

The absorption of desirudin was slow but complete through the SC route. In general, C_{max} and AUC increased in a dose-proportional manner irrespective of the route of administration. Following IV administration of desirudin, elimination from plasma was rapid in the initial phase and slow in the terminal phase, with 90% of the dose disappearing from the plasma within 2 hrs of the injection. Plasma concentrations declined with mean terminal elimination half-life of 2 to 3 hrs. After SC administration mean terminal half-life was about 2 hrs. Dose-independent volume of distribution at steady state of 0.25 L/kg, suggests that desirudin stays in the circulation (central compartment) and the extracellular space. It was demonstrated that desirudin is primarily eliminated and metabolized by the kidney. Two metabolites of desirudin [desirudin minus one (Gln_{65}) and two (Leu_{64}-Gln_{65}) C-terminal amino acids] were detected in urine in trace amounts only. The stepwise degradation of the C-terminus of r-hirudin catalyzed by carboxypeptidase was the only metabolic process observed. Excretion of desirudin and its metabolites accounted for about ~50% of the dose when given IV. The two metabolites constituted < 7% of the material recovered in the urine. Only 37% was recovered in urine using the SC route.

Pharmacokinetics of desirudin was evaluated in subjects with mild, moderate and severe renal insufficiency. $AUC_{0\text{-}60hr}$ for aPTT prolongation was increased by 3- and 9-fold in subjects with moderate and severe renal impairment. In elderly subjects, maximum aPTT prolongation was higher and the C_{max} and AUC values calculated based on non-specific ELISA assay were higher compared to young volunteers, however, no difference was observed when corrected for creatinine clearance. Five drug-drug interaction studies were conducted in healthy volunteers with drugs affecting platelet function (acetylsalicylic acid and piroxicam) or drugs that have the potential to interfere with anticoagulant effects of desirudin (heparin, warfarin, and DDAVP, a vasopressin analog). No dosage adjustment can be recommended based on pharmacokinetic data obtained from the five drug-drug interaction studies with desirudin, because none of these drugs significantly altered the pharmacokinetics of desirudin. However, Piroxicam was investigated at the dose of 10 mg/day which is half the usual dose of 20 mg/day. Desirudin may potentiate the effect of large molecular weight dextrans given in large doses and may cause hemorrhage by impairing platelet function. Drug-drug interaction has not been studied with this combination, therefore co-administration of desirudin and dextrans is contraindicated during or immediately after surgery.

Recommendation: Clinical Pharmacology and Biopharmaceutics information submitted under this NDA is acceptable from OCPB perspective.

Comments to the sponsor:

1. Labeling should be modified to indicate that PK parameters calculated were based on plasma concentration data obtained by a non-specific ELISA method, that does not discriminate between native desirudin and its metabolites. The sponsor should attempt to develop a specific assay method such as ——— assay to analyze the plasma and urine samples and update the label accordingly.

2. Desirudin has not been investigated in hepatic insufficiency. As suggested by the sponsor, although desirudin is not significantly metabolized by the liver, severe hepatic impairment may alter anticoagulant effect of desirudin due to defects resulting from reduced generation of vitamin K-dependent coagulation factors. Thus, a study in hepatic impairment is recommended as a Phase 4 commitment.

3. For dose adjustment in moderate and severe renal impaired patients $AUC_{0\text{-}60hr}$ for aPTT prolongation should be considered and accordingly reduced by 3- and 9-fold, respectively. Due to the absence of a specific assay procedure aPTT prolongation is a more reliable estimate of desirudin exposure.

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

8/28/2000
Date

Sam Haidar, R.Ph., Ph.D.
Pharmacometrician

8/28/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D.

c.c. /NDA 21-271
/HFD-180 (Division files, BStrongin)
/HFD-870 (SDoddapaneni, HMalinowski, SRoy, SHaidar)
/HFD-850 (Plee, LLesko)
/CDR (ZZadeng)

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Question Based Review

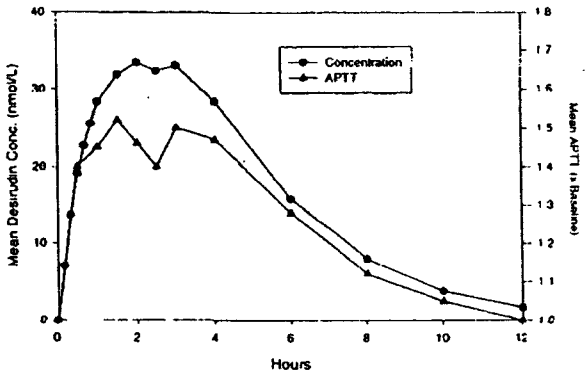
Analytical Method

Are the analytical methods used for assay of desirudin adequately validated?

[ ]

What is the dose/exposure response (effectiveness, safety) relationship?

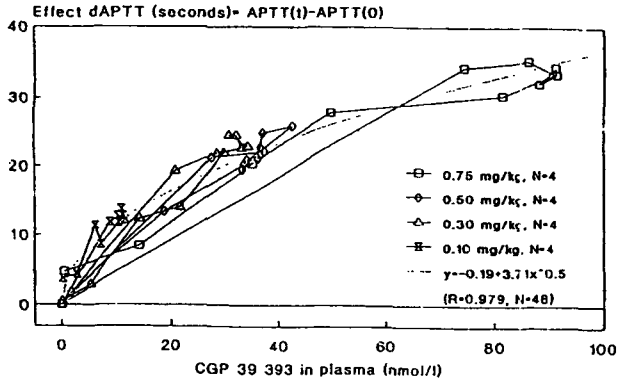
- APTT (activated partial thromboplastin time) values closely paralleled plasma conc. APTT fell rapidly following IV injections, but as the plasma conc. declined less rapidly following SC injection the aPTT levels were also maintained for up to 6 – 8 hr post injection.



- Comparing SC and IV, equality of effect reached 2-3 hrs after drug administration.
- $dAPTT_{max}$ (maximum change in activated partial thromboplastin time) and AUC_{effect} was dose dependent, but increase was less than dose proportional, i.e. dose-normalized parameters decreased with increasing dose.

- Increase in $daPTT_{max}$ and AUC_{effect} was about proportional to the square root of dose (R = 0.795 & 0.814, resp.).

- dAPTT was shown to be proportional to the square root of the plasma drug concentration (R = 0.979). *See pharmacometric review (Appendix) for additional details*



- Based on hysteresis plot there was no evidence of clockwise looping (developing tolerance), nor counter-clockwise looping (delayed or prolonged activity). However, mean concentrations were plotted against mean aPTT values. Individual conc. should've been plotted against corresponding aPTT values to unmask hysteresis phenomenon that may exist. *See pharmacometric review (Appendix) for additional details.*
- APTT prolongation values in healthy volunteers were quite comparable to those observed in patients undergoing elective hip replacement.
- Dose dependent inhibition of post-operative thromboembolic events were observed in the fixed dose range of 10 – 20 mg. Occurrence of excessive bleeding was also dose dependent. A fixed SC dose of 40 mg given twice daily for 10 consecutive days produced excessive bleeding in these patients, whereas, fixed doses of 15 and 20 mg had less bleeding complications and were equally effective.

Safety:	Efficacy (thromboembolic events):
40 mg (~0.6 mg/kg): 3 pts major/ serious bleeding complications	20 mg (~0.3 mg/kg): 10%
20 & 15 mg (~0.3 & 0.2 mg/kg): 1 pt major/ serious bleeding complications	15 mg (~0.2 mg/kg): 9%
	10 mg (~0.14 mg/kg): 42%

What is the PK behavior of desirudin in healthy subjects?

Absorption:

- The absorption is almost complete when administered by SC route at doses of 0.3 mg/kg or 0.5 mg/kg.
- Absorption is slow through the SC route taking 4.6 hrs for half the dose to enter circulation.
- In general, C_{max} and AUC increased in a dose-proportional manner in the dose range of 0.1 – 0.75 mg/kg, when desirudin was administered by the subcutaneous route.

Distribution:

- The plasma concentrations decreased multi-exponentially following IV administration of desirudin.
- Dose-independent volume of distribution at steady state of 0.25 L/kg, suggests that desirudin stays in the circulation (central compartment) and the extracellular space.

- Results of plasma protein binding varied between 15% and 80%, depending on the method used and were difficult to interpret.
- It is believed that desirudin binds specifically and directly to thrombin forming a non-covalent Thrombin-hirudin complex (THC) with an inhibition constant of 2.6×10^{-13} M. AUC of THC represents only about 1% of AUC of the free desirudin.

Metabolism:

- It was demonstrated that desirudin is primarily eliminated and metabolized by the kidney.
- Two metabolites of desirudin [desirudin minus one (Gln_{65}) and two (Leu_{64}-Gln_{65}) C-terminal amino acids] were detected in urine in trace amounts only. The stepwise degradation of the C-terminus of r-hirudin catalyzed by carboxypeptidase was the only metabolic process observed.
- Excretion of desirudin and its metabolites accounted for about ~50% of the dose when given IV. The two metabolites constituted < 7% of the material recovered in the urine. Only 37% was recovered in urine using the SC route.

Elimination:

- Following IV administration, elimination from plasma was rapid in the initial phase and slow in the terminal phase, with 90% of the dose disappearing from the plasma within 2 hrs of the injection.
- Plasma concentrations declined with mean terminal elimination half-life of 2 to 3 hrs.
- After SC administration mean terminal half-life was about 2 hrs.
- Kidney is the primary route of elimination for desirudin. Total plasma clearance (~150 ml/min) was greater than glomerular filtration rate, whereas the renal clearance (~55 ml/min) was less than the creatinine clearance.

Note: These estimates are based on a non-specific ELISA procedure and thus represent mixture of parent compounds and its metabolites.

How does desirudin pharmacokinetics compare in patients and healthy volunteers?

Peak plasma concentrations observed in patients undergoing hip replacement were comparable to that observed in healthy subjects.

Trial#	Dose	Peak Conc. (nmol/L)
RH/PT 3 (patients)	20 mg fixed	38.2 ± 10
RH/ET 23 (patients)	20 mg fixed	36.3 ± 19.7
RH/ET 9 (healthy volunteers)	21 mg (0.3 mg/kg)	39.1 ± 8.4

Note: These estimates are based on a non-specific ELISA procedure and thus represent mixture of parent compounds and its metabolites.

The mean trough and peak aPTT prolongation values observed in these patients were similar to those obtained in healthy volunteers.

Trial#	Dose	Trough aPTT prolongation (x baseline)	Peak aPTT prolongation (x baseline)
RH/ET 23 (patients)	20 mg fixed	1.17 ± 0.17	1.42 ± 0.28
RH/ET 9 (healthy volunteers)	21 mg (0.3 mg/kg)	1.11 ± 0.07	1.54 ± 0.18

What degree of change in desirudin pharmacokinetics necessitates a change in dosing recommendation?

A fixed SC dose of 40 mg desirudin (~0.57 mg/kg) caused serious bleeding complications in patients undergoing total elective hip replacements. Serious bleeding also occured at the fixed doses of 15 and 20 mg, whereas no adverse events were reported in healthy volunteers at these doses. aPTT prolongation values were similar in patients and healthy volunteers. APTT prolongation is probably not an appropriate surrogate marker from the safety perspective. Thus, a conservative dose adjustment may be the best approach in treating these patients. Dosage adjustment based on creatinine clearance should be considered in order to avoid accidental over-exposure in these patients. *[See pharmacometric review (Appendix) for further details.*

Special Population

What is the effect of renal impairment on the pharmacokinetics of desirudin? Is dose adjustment necessary in renal impaired patients?

- Close correlation between total plasma clearance and creatinine clearance was observed indicating kidney as the predominant route of elimination.
- Within the range of creatinine clearance (CrCL) observed in patients undergoing hip replacement (28 – 171 ml/min), the estimated total plasma clearance (CL) was related to renal clearance (Clr) such that: **CL (L/h) = 10.93 + 1.12 (CrCL – 80)/10**
- Mean area under the plasma concentration –time curve increased by a factor of 1.15, 2.83, and 7.0 for subjects with mild, moderate, and severe renal failure, respectively, compared with healthy subjects.
- Mean $AUC_{0\text{-}60hr}$ (× baseline.hr) for aPTT prolongation increased by 3- and 9- fold for subjects with moderate and severe renal failure, respectively.
- It appears dose reductions recommended by the sponsor in renal failure patients were based on changes in pharmacodynamic measures rather than the pharmacokinetics parameters. This is reasonable because pharmacokinetic estimates not be considered as reliable due to the non-specific assay procedure.
- However, $AUC_{0\text{-}60hr}$ values for aPTT prolongation should have been considered in moderate and severe renal failure subjects rather than $AUC_{0\text{-}36hr}$ values. Based on the corrected data (to 1 mg/kg) 9-fold reduction in dose should be recommended in severe renal failure and 3-fold reduction in moderate renal failure patients.

What is the effect of hepatic impairment on the pharmacokinetics of desirudin? Is dose adjustment necessary in patients with hepatic impairment?

Desirudin has not been investigated in hepatic insufficiency. As suggested by the sponsor, although desirudin is not significantly metabolized by the liver, severe hepatic impairment may alter anticoagulant effect of desirudin due to defects resulting from reduced generation of vitamin K-dependent coagulation factors. Thus, a study in hepatic impairment is recommended as a Phase 4 commitment.

How does desirudin pharmacokinetics compare between males and females?

Population pharmacokinetics conducted in 301 patients undergoing elective total hip replacement indicate that gender do not affect the systemic clearance of desirudin when it is corrected for renal creatinine clearance. *[See pharmacometric review (Appendix) for further details].*

How does desirudin pharmacokinetics compare between young adults and the elderly?

- AUC, C_{max}, T_{max}, and $T_{1/2}$ values were increased in elderly compared to young volunteers.
- Total plasma clearance was reduced (28%) in elderly compared to young volunteers. These young volunteers were not part of the same study, but received the same dose (0.3 mg/kg) in a separate study (RH/ET10).
- There was a tendency for plasma clearance to decrease in parallel with decreasing creatinine clearance. Assuming desirudin is taken up by the kidney tubule and are irreversibly lost, the GFR is a measure of true clearance. Then the difference between total plasma clearance (110 ml/min) and creatinine clearance (52 ml/min) will represent non-renal clearance of desirudin. Non-renal clearance would then account for ~53% in elderly compared to ~20% in young population.
- PK-PD relationship was not different in elderly compared to young healthy volunteers.
- Population pharmacokinetics conducted in 301 patients undergoing elective total hip replacement indicate that age do not affect the systemic clearance of desirudin when it is corrected for renal creatinine clearance. *[See pharmacometric review (Appendix) for further details].*
- Dosage adjustment recommendation should be consistent with renal failure patients and should be reduced by 3- and 9-fold in elderly patients with creatinine clearance < 60 ml/min and < 30 ml/min, respectively.

Drug-Drug Interaction

Does any co-administered drug affect the PK of desirudin, requiring a dosage adjustment for desirudin?

- Five drug-drug interaction studies were conducted in healthy volunteers with drugs affecting platelet function (acetylsalicylic acid and piroxicam) or drugs that have the potential to interfere with anticoagulant effects of desirudin (heparin, warfarin, and DDAVP, a vasopressin analog)
- There was no effect of DDVAP on the pharmacokinetics of desirudin. However, it was shown that an infusion of DDVAP can partially reverse the desirudin induced increase in aPTT.
- The pharmacokinetics of desirudin was not altered by concomitant infusion of heparin.
- Warfarin did not significantly affect the pharmacokinetics of desirudir. There was an additive effect of desirudin on aPTT and PT (INR) when co-administered with warfarin, however did not raise safety issues and was clinically significant in healthy volunteers.
- No significant pharmacokinetic interaction between desirudin and piroxicam (10 mg/daily) were observed. Neither was there any obvious alteration of the anticoagulant effect of desirudin. However, only half the usual daily dose of 20 mg piroxicam was administered.
- Acetylsalicylic acid (ASA) had no effect on the plasma pharmacokinetics of desirudin following an IV infusion. Administration of ASA had no effect on aPTT and PT values produced by IV infusion of desirudin. Prolonged bleeding times observed in three subjects may not be of clinical significance in these subjects but may be a safety issue in subjects who are susceptible to GI ulceration and bleeding by COX inhibitiors.

- No dosage adjustment can be recommended based on pharmacokinetic data obtained from the five drug-drug interaction studies with desirudin.
- Desirudin may potentiate the effect of large molecular weight dextrans given in large doses and may cause hemorrhage by impairing platelet function. Drug-drug interaction has not been studied with this combination, therefore co-administration of desirudin and dextrans is contraindicated during or immediately after surgery.

Bioequivalence

What bioavailability and bioequivalence data are available to assess the quality of the subcutaneous formulation of desirudin?

- An open-label, randomized, cross-over, single-center, single-dose bioequivalence trial was conducted in 12 healthy male volunteers who received SC doses of 15 mg desirudin as the F4 (new) and F1 (clinical trial) formulations.
- In the new formulation F4, the only change, [redacted] by $MgCl_2$, whereas the composition and volume of the solvent used for reconstitution remained the same.
- Similar plasma levels, pharmacokinetic parameters and pharmacodynamic effects were observed with F1 and F4 formulations. The conc.-response relationship were also investigated using NONMEM analysis and were not found different for formulation F4 compared with formulation F1.
- Desirudin $AUC_{0-\infty}$ Ratio (F4/F1) = 0.967
  90% C.I.: 0.93 – 1.07
- C_{max} Ratio (F4/F1) = 0.927
  90% C.I.: 0.85 – 1.04
- Ratio of AUC_{0-24h} for aPTT prolongation (F4/F1) = 0.9786
  90% C.I.: 0.9499 – 1.0081
- Ratio of $dAPTT_{max}$ (F4/F1) were not provided

Labeling Review

Following labeling changes are recommended in the proposed package insert for **Desirudin for Injection** in sections that are relevant to OCPB. Changes are indicated by strikethroughs (deletions) and underlined (additions) text:

CLINICAL PHARMACOLOGY

Mechanism of Action: Desirudin is a [redacted] selective inhibitor of free circulating and clot-bound thrombin. The anticoagulant properties of desirudin are demonstrated by its ability to prolong the clotting time of human plasma. One molecule of desirudin binds to one molecule of thrombin and thereby blocks the thrombogenic activity of thrombin. As a result, all thrombin-dependent coagulation assays are affected. Activated partial thromboplastin time (aPTT) is [redacted] measure of the anticoagulant activity of desirudin and increases in a dose-dependent fashion. The pharmacodynamic effect of desirudin on proteolytic achvity of thrombin was [redacted] assessed as an increase in aPTT. A mean peak aPTT prolongation of about [redacted] times baseline value was observed following a [redacted] b.i.d. injection of 15 mg desirudin. Thrombin time (TT) frequently exceeds 200 seconds even at low plasma concentrations of desirudin, which renders this test unsuitable for routine monitoring of [redacted]

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Appendix II

Single Dose Studies [Subcutaneous] In Healthy Volunteers

Report #	Design	Results	Discussion
B 6/1991 B 9/1991 (RH/ET8)	Open, comparative, single-dose trial in 8 healthy volunteers at four dose levels (SC bolus of 0.1, 0.3, 0.5, and 0.75 mg/kg) with 4 subjects per dose level	**Analytical method** ELISA: LOQ: ~~/~~ nmol/L LOD: 0.5 nmol/L TCA values were higher than ELISA values at and near baseline and lower at high concentrations **Pharmacokinetics** Dose (mg/kg) 0.1 0.3 0.5 0.75 C_{max} (nmol/L) AUC (nmol/L.hr) 109 271 509 728 T_{max} (hr) 2.5 – 3.3 hr Cl (ml/min/kg) 2.3 – 2.7 $T_{1/2}$ (hr) 2.0 – 2.4 hrs MATsc = MRTsc – MRTiv = 4.6 hrs **Pharmacodynamics** $dAPTT_{max}$ (sec): 14, 25, 28, 36 $AUC_{0\text{-}24h}$ (hr.sec): 166, 197, 330, 368	Dose proportionality was not clearly demonstrated. Although clearance was independent of dose, dose normalized AUC appeared lower for 0.5 mg/kg and C_{max} appeared higher at 0.75 mg/kg (Figure 1 & 2). Bioavailability was 87%. Slow absorption through SC route taking 4.6 hrs for half the dose to enter circulation. $dAPTT_{max}$ and AUC_{effect} was dose dependent, but increase was less than dose proportional, i.e. dose-normalized parameters decreased with increasing dose [Figure 4]. Increase in $daPTT_{max}$ and AUC_{effect} was about proportional to the square root of dose (R = 0.795 & 0.814, resp.) [Figure 4] daPTT was shown to be proportional to the square root of the plasma drug concentration (R = 0.979) [Figure 3]. Comparing SC and IV, equality of effect reached 2-3 hrs after drug administration [Figure 1]
B 23/1990 (RH/ET3)	Open comparative single dose trial of two single SC doses of either 0.1 and 0.3 mg/kg or 0.2 and 0.4 mg/kg on non-consecutive days in 16 healthy volunteers	**Analytical method** ELISA: LOQ: ~~/~~ nmol/L LOD: 0.5 nmol/L **Pharmacokinetics** Dose (mg/kg) 0.1 0.2 0.3 0.4 C_{max} (nmol/L) AUC (nmol/L.hr) 150 304 484 575 Cl (ml/min/kg) 1.5 – 1.7 $T_{1/2}$ (hr) 2.0 – 2.4	C_{max} and AUC are dose proportional [Figure 5] Good correlation between ELISA and aPTT values (R = 0.84) Based on hysteresis plot no evidence of clockwise looping (developing tolerance), nor for counter-clockwise looping (delayed or prolonged acitivity) [Figure 6]. However, mean concentrations were plotted against mean aPTT values. Individual conc. should've been plotted against corresponding aPTT values to unmask hysteresis phenomenon that may exist.

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B90/1989 UK R6/1989 CRB R 10/1993 (RH/E10)	Open balanced cross-over trial comparing one SC and one IV administration of two dose levels in eight healthy male volunteers (0.3 and 0.5 mg/kg)	**Analytical method** ELISA: LOQ: ✎ nmol/L LOD: 0.2 nmol/L **Pharmacokinetics** IV Dose (mg/kg) 0.3 0.5 C_{max} (nmol/L) 455 867 AUC (nmol.hr/L) 342 641 Cl (ml/min) 152 139 $T_{1/2}$ (hr) 1 – 2 0.8 –6.5 SC Dose (mg/kg) 0.3 0.5 C_{max} (nmol/L) AUC (nmol.hr/L) 344 601 $T_{1/2}$ (hr) 2 – 3 2 – 4 **Urinary excretion** At both dose levels, the mean total urinary excretion was close to 50 and 37% of the IV and SC dose, respectively. Most of the excretion occurred within the first 2 hr after IV dose, whereas the excretion was delayed after SC administration till 8 – 10 hr	C_{max} and AUC are dose proportional [Figure 7 & 9]. Max aPTT prolongation: 2.6 – 3.1 and 2.9 – 3.5 times baseline following IV 0.3 and 0.5 mg/kg, respectively. 1.5 – 1.7 and 1.5 – 1.8 times baseline following SC 0.3 and 0.5 mg/kg, respectively. aPTT values closely paralleled plasma conc. aPTT fell rapidly following IV injections, but as the plasma conc. declined less rapidly following SC injection the aPTT levels were also maintained for up to 6 – 8 hr post injection. The measured total plasma clearance of desirudin was always slightly greater than GFR, whereas, the apparent renal clearance of desirudin was always less than the creatinine clearance [Figure 8]. Assuming desirudin is taken up by the kidney tubule and are irreversibly lost, the GFR is a measure of true clearance. Then the difference between total plasma clearance (150 ml/min) and creatinine clearance (122 ml/min) will represent non-renal clearance of desirudin. In this group of subjects non-renal clearance accounts for ~20%. Urinary excretion of desirudin is lower after SC administration compared to IV. The reason for this unclear since the plasma data showed complete absorption of the SC doses. Overloading of tubular reabsorption pathway may be a plausible explanation.

Multiple Dose Studies [Subcutaneous]
In Healthy Volunteers

RH/ET 9	Open, comparative, multiple-dose trial in 8 healthy volunteers given SC injection of 0.3 or 0.5 mg/kg twice daily for 6 consecutive days with 4 subjects per dose level	**Analytical method** ELISA: Two-step TCA values closely followed ELISA values. Peak conc. was lower with TCA assay than with ELISA. **Pharmacodynamics** $daPTT_{max}$ (sec) 0.3 mg/kg: 56.6 (1.69 X baseline) 0.5 mg/kg: 66.7 (2.10 X baseline) **Pharmacokinetics** *Peak concentrations* (nmol/L) 0.3 mg/kg: — 0.5 mg/kg: — *Trough concentrations* (nmol/L) 0.3 mg/kg: — 0.5 mg/kg: —	Effect on aPTT was dose dependent. Plasma conc. correlated with the degree of anticoagulation evaluated by aPTT.
B 2/1992 (RH/ET6)	Open, comparative trial in 9 male and 7 female given SC t.i.d. for three days at the two dose levels 0.3 or 0.5 mg/kg	**Analytical Method** ELISA: LOQ: — nmol/L LOD: 0.5 nmol/L **Pharmacokinetics** *Peak concentrations* (nmol/L) 0.3 mg/kg: 76 ± 16 0.5 mg/kg: 121 ± 34 *Trough concentrations* (nmol/L) 0.3 mg/kg: 12 ± 2 0.5 mg/kg: 39 ± 23	Steady-state conc. reached with administration of the 2nd dose and no further accumulation observed. Peak conc. increased proportionally with dose, but trough conc. increased more than proportionally to the dose. Trough and peak concentrations for 0 3 mg/kg were acceptably simulated by convolution of the experimental elimination function with an absorption of first order kinetics and a half-life of 1.65 hrs. However, trough concentrations were higher than predicted by the simulation for 0.5 mg/kg (Figure 10)

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Multiple Dose Studies [Subcutaneous]
In Patients

BPK(F) 1994/022 (RH/E 23)	Multi-center, double-blind, randomized, heparin-controlled, dose-finding trial in 1119 patients undergoing a total elective hip replacements who received bid SC injection over 11 days at the doses of 10 mg (n=283), 15 mg (n=277), 20 mg (n=282) and 5000 IU, tid SC heparin over 11 days (n=277)	**Analytical method** ELISA: LOQ: [redacted] nmol/L Precision: [redacted] Accuracy: [redacted] **Pharmacokinetics** Dose (mg) / Peak conc. (nmol/L) / Trough conc. (nmol/L) 10 / 20.6 ± 14.3 / 5.6 ± 4.6 15 / 30.9 ± 18.4 / 9.7 ± 10.2 20 / 36.3 ± 19.7 / 12.2 ± 9.2 Peak conc. measured 2 to 3 hr after injection Trough conc. measured just prior to morning injection **Pharmacodynamics** (aPTT prolongation) Dose (mg) / Peak (× baseline) / Trough (× baseline) 10 / 1.27 ± 0.20 / 1.09 ± 0.16 15 / 1.38 ± 0.29 / 1.14 ± 0.17 20 / 1.42 ± 0.28 / 1.17 ± 0.17	Peak and trough levels increased with increase in dose. Peak plasma conc. were comparable to that observed in healthy subjects at the dose of 21 mg (0.3 mg/kg bid to subject of 70 kg) where peak conc. was 39.1 ± 8.4 nmol/L, whereas trough conc. was lower in healthy volunteers (3.4 ± 1.9 nmol/L). aPTT prolongation values were also similar to the healthy subjects [trough: 1.11 ± 0.07 (× baseline) and peak: 1.54 ± 0.18 (× baseline)]
RH/PT 3 CRB R 31/1992	Open pilot ascending dose finding trial of four dose levels (10, 15, 20, and 40 mg SC twice daily for 10 days) in 48 patients undergoing total elective hip replacement	**Analytical method** ELISA: LOQ: [redacted] nmol/L Precision: [redacted] Accuracy: [redacted] **Pharmacokinetics** Dose (mg) / Peak conc. (nmol/L) / Trough conc. (nmol/L) 10 / 23 ± 9.1 / 5.7 ± 4.6 15 / 35.5 ± 8 / 10.7 ± 10.2 20 / 38.2 ± 10 / 10.8 ± 9.2 40 / 87.2 / 37.1 Peak conc. measured 2 to 3 hr after injection Trough conc. measured just prior to morning injection **Safety:** 40 mg (~0.6 mg/kg): 3 pts major/ serious bleeding complications 20 & 15 mg (~0.3 & 0.2 mg/kg): 1 pt major/ serious bleeding complications **Efficacy** (thromboembolic events): 20 mg (~0.3 mg/kg): 10% 15 mg (~0.2 mg/kg): 9% 10 mg (~0.14 mg/kg): 42%	Trough and peak concentrations were dose dependent, generally increasing with increasing doses. Dose dependent inhibition of post-operative thromboembolic events in the fixed dose range of 10 – 20 mg. Occurrence of excessive bleeding was also dose dependent

Single Dose Studies [Intravenous]
In Healthy Volunteers

B 82/1989 (RH/ET7)	Open, comparative, single-dose trial in one center where 8 subjects received single IV doses of desirudin at two of the four dose levels 0.1, 0.3, 0.5, and 1.0 mg/kg on consecutive days (day 1 and day 3), i.e. 4 subjects/dose level. Six additional subjects received 1.0 mg/kg only.	**Analytical method** ELISA: LOQ: — nmol/L LOD: 0.2 nmol/L **Pharmacokinetics** Dose (mg/kg) 0.1 0.3 0.5 1.0 1.0 C_{5min} (nmol/L) 166 515 940 1858 2069 AUC_{0-24h} (nmol/L.hr) 124 348 597 1140 1125 Cl (ml/min/kg) 2.0 2.1 2.1 2.1 2.1	The plasma concentrations decreased multi-exponentially. Elimination from plasma very rapid in the initial phase and slow in the terminal phase. C_{max} and AUC were dose proportional [Figure 11].
B 103/1990 (RH/ET1)	Single IV bolus injections at 4 dose levels 0.1, 0.3, 0.5, and 1.0 mg/kg were given to 16 healthy volunteers. Each of the 16 volunteers received two of the four doses	**Analytical method** ELISA: LOQ: — nmol/L LOD: 0.2 nmol/L Upper limit of detection by 2-step TCA method was 72 nmol/L. Majority of the plasma samples could not be measured with the assay. Correlation between TCA and ELISA values were poor at concentrations higher than 72 nmol/L. **Pharmacokinetics** Dose (mg/kg) 0.1 0.3 0.5 1.0 C_{5min} (nmol/L) 159 407 717 1324 AUC (nmol/L.hr) 118 313 572 1012 Cl (ml/min/kg) 2.1 2.3 2.1 2.5 MRT (hr) 2.1 1.8 2.0 1.7	Plasma kinetics of desirudin was linear. C_{max} and AUC increased in a dose proportional manner [Figure 12].
B76/1989 (RH/ET 2)	Open, comparative, single-dose trial in 12 healthy volunteers at three dose levels (IV infusion of 0.1, 0.3, and 0.5 mg/kg/hr for 6 hrs) with 8 subjects per dose level	**Analytical method** ELISA: LOQ: / nmol/L LOD: 0.3 nmol/L **Pharmacokinetics** Dose (mg/kg) 0.1 0.3 0.5 C_{ss} (nmol/L) 88 164 301 AUC (nmol/L.h) 635 1317 2295 CL (ml/min/kg) 2.8 3.2 2.5	C_{ss} & AUC were dose-proportional, CL was independent of dose (Figure 13).

Single Dose Studies [Intravenous]
In Patients

US 01	Single-blind, placebo-controlled, ascending-dose (0.02, 0.05, 0.1, 0.2, and 0.3 mg/kg/h) given as 6-hr infusion in 41 patients with stable coronary artery disease	**Pharmacokinetics** Dose (mg/kg) / C_{max} (nmol/L) / AUC (nmol.h/L) 0.02 / 25.8 ± 8.5 / 176 ± 68 0.05 / 67.6 ± 20 / 388 ± 139 0.10 / 122 ± 19 / 792 ± 145 0.20 / 229 ± 38 / 1410 ± 176 0.30 / 317 ± 65 / 2130 ± 483 Urinary excretion (%) / Total CL ml/min / Renal CL ml/min 0.02 mg/kg: 44.3 ± 15.1 / 179 ± 89 / 71 ± 24 0.05 mg/kg: 43.3 ± 7.4 / 167 ± 42 / 73 ± 23 0.1 mg/kg: 48.9 ± 6.2 / 180 ± 17 / 88 ± 17 0.2 mg/kg: 47.3 ± 12.8 / 188 ± 48 / 87 ± 26 **Pharmacodynamics** *Peak Median Ratio of aPTT to baseline:* 0.02 mg/kg: 1.04 – 1.85 0.05 mg/kg: 1.74 – 2.37 0.1 mg/kg: 2.09 – 2.62 0.2 mg/kg: 2.45 – 3.04 0.3 mg/kg: 2.37 – 3.37	aPTT values were prolonged in a dose-related manner (Figure 14). Urinary excretion in these patients were similar to healthy volunteers who received IV bolus of desirudin.

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Drug-Drug Interaction

UK R3/1991 CRB R 43/1991 (RH/E 14)	Placebo-controlled study in which 12 healthy male volunteers received either 0.3 mg/kg IV bolus desirudin + 0.3 mg/kg/h IV infusion for 4 hrs or 0.2 mg/kg IV bolus + 0.2 mg/kg/h IV infusion for 4 hrs. After 2 hrs from start of infusion, 0.9% saline was infused for 15 min followed 1 hr later by DDAVP (vasopressin analog) infusion at the rate of 1.2 µg/kg/hr for 15 min (total dose of 0.3 µg/kg) or	**Analytical method** ELISA: LOQ: ~~/~~ nmol/L LOD: 0.2 nmol/L TCA: LOQ: ~~—~~ ll/l. Although good correlation was observed between ELISA & TCA values, TCA values were higher than ELISA values in general. **Pharmacokinetics** DDAVP showed not effect on the plasma pharmacokinetics of desirudin [Figure] Dose (mg/kg/h) 0.3 0.2 Cmax (nmol/L) 287 ± 36 185 ± 29 Median Tmax (hr) 3.74 2.00 AUC (nmol.hr/L) 1275 ± 156 861 ± 164 **Pharmacodynamics** aPTT levels fell rapidly after start of the DDAVP infusion [Figure] Factor VIII:C levels increased dramatically to 5 × baseline in presence of lower dose desirudin infusion and to 4.3 × baseline in presence of the higher dose desirudin infusion [Figure not shown] PT values increased slightly in some patients at the higher dose desirudin infusion after the start of DDAVP infusion, but were not effected in the patients on lower dose desirudin infusion [Figure not shown]	There was no effect of DDVAP on the pharmacokinetics of desirudin. However, it was shown that an infusion of DDVAP can partially reverse the desirudin induced increase in aPTT [Figure 15] and can dramatically increase factor VIII:C levels depending on the rate of ongoing desirudin infusion. APPEARS THIS WAY ON ORIGINAL

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CRB R12/1992 (US 03)	Open-label, single-center, ascending-dose study given as IV bolus alone and in combination with heparin in healthy volunteers. A total of 19 subjects were randomized to treatment: 0.1 (n=4), 0.03 (n=4), 0.05 (n=6), and 0.1 mg/kg (n=5). First IV bolus was given alone. The 2nd IV bolus was given in addition to IV infusion of heparin (bolus of 5000 Units followed by infusion of 1000 Units/h) which was titrated to maintain the subject's aPTT at 1.5 to 2 times the baseline	**Analytical method** ELISA LOQ: [redacted] nmol/L in plasma **Pharmacokinetics** Mean C5 values (nmol/L): mg/kg alone w/heparin 0.01 10.9 10.8 0.03 42.9 43.1 0.05 72.3 68.2 0.10 128.2 141.2 Mean AUC values (nmol.hr/L): mg/kg alone w/heparin 0.02 4.7 4.5 0.03 28.7 30.1 0.05 34.6 37.1 0.10 88 83.4 $T_{1/2}$ (hr): 1.5 – 2.4 (alone) 1.6 – 2.3 (w/heparin) *Dose normalized C5 min (nmol/L/nmol)* Desirudin alone: 0.128 ± 0.047 With heparin: 0.128 ± 0.026 *Dose normalized AUC (nmol.h/L/nmol)* Desirudin alone: 0.073 ± 0.031 With heparin: 0.074 ± 0.028	Plasma concentrations decreased in a bi-phasic manner. C5 and AUC values increased in linear fashion with increasing doses [Figure 16]. The pharmacokinetics of desirudin was not altered by concomitant infusion of heparin. Mean plasma profiles obtained after each dose were similar with desirudin alone and in combination with heparin. Slight tendency of dose normalized AUC values to increase with increasing doses (Figure 18)
UK R1/1994 (RH/E35)	Open, non-randomized, single centre trial, two treatment period study [warfarin alone and then single dose of desirudin immediately followed by desirudin (0.3 mg/kg SC bid for 3 days + warfarin (2 × 5 mg daily oral)] in 12 healthy volunteers	**Analytical method** ELISA: Accuracy: [redacted] Precision: [redacted] **Pharmacokinetics** Alone w/warfarin AUC (nmol.h/L) 349±53 359±46 $T_{1/2}$ (hr) 1.9 1.7 Cl (ml/min) 155 ± 20 151 ± 13 **Pharmacodynamics** *aPTT difference between desirudin alone and with warfarin* Median difference of Absolute value: 18.3 secs Ratio to baseline: 0.5 *PT difference between desirudin alone and with warfarin* Median difference of Absolute value: 1.1 INR (International Normalized Ratio) Ratio to baseline: 0.8	Warfarin did not significantly affect the pharmacokinetics of desirudin. There was an additive effect of desirudin on aPTT and PT (INR) when co-administered with warfarin, however did not raise safety issues and was clinically significant in healthy volunteers

RH/E34	Double-blind, randomized, placebo-controlled crossover study in 12 healthy volunteers where each volunteer received piroxicam (10 mg capsule) or placebo oral dose for twelve days, followed by an infusion of desirudin (0.1 mg/kg/hr for 6 hr)	**Analytical method** ELISA: LOQ in plasma — nmol/L LOQ in urine — nmol/L Precision: — in plasma — in urine Accuracy: — in plasma — in urine Total amount of desirudin measured in urine was in good agreement with that measured by HPLC **Pharmacokinetics** Placebo / w/piroxicam Mean Css (nmol/L): 82 ± 9.5 / 80.5 ± 10.5 Mean AUC_{0-24h} (nmol.h/L): 542 ± 67 / 542 ± 72 $T_{1/2}$ (hr): 1.95 / 2 Urinary recovery 0 – 2 hr (nmol): 522 ± 277 / 588 ± 257 up to 24 hr (nmol): 2720 ± 529 (43%) / 2590 ± 665 (41%) **Pharmacodynamics** Max. aPTT were *AUC_{0-24h} for aPTT prolongation* Placebo: 31.4 ± 10 sec/sec.hr w/piroxicam: 32.1 ± 5.3 sec/sec.hr	Under the conditions of this trial no significant pharmacokinetic interaction between desirudin and piroxicam were observed. Neither was there any obvious alteration of the anticoagulant effect of desirudin [Figure]. However, half the usual daily dose of 20 mg was studied in this trial. The concentration effect relationship between the mean desirudin conc. and aPTT prolongation were similar for both treatments and did not show any hysteresis phenomena [Figure 17]
UK R5/1990 (RH/ET4)	Double-blind, balanced, two-way cross-over PK-PD study in 12 healthy male volunteers who received either single 300 mg oral capsule of acetylsalicylic acid (ASA) or single oral placebo capsule on day 1 and day 2 followed by 0.3 mg/kg/h IV infusion of desirudin for 6 hrs only on day 2.	**Analytical method** ELISA: LOQ — nmol/L LOD - 0.2 nmol/L **Pharmacokinetics** With ASA / With Placebo AUC_{0-24hr} (nmol.h/L): 1571 ± 311 / 1568 ± 243 C_{ss} (nmol/L): 245 ± 70 / 257 ± 56 Cl (ml/min/kg): 2.9 ± 0.7 / 2.8 ± 0.4 **Pharmacodynamics** With ASA / With Placebo Max aPTT prolongation (3-6 hr after infusion) (× baseline): 2.4 ± 0.1 / 2.5 ± 0.2 Max PT (INR): 1.7 ± 0.1 / 1.7 ± 0.2 Both aPTT and PT returned to baseline within 24 hr. Note: In three subjects bleeding times were prolonged significantly when ASA was co-administered with desirudin.	ASA had no effect on the plasma pharmacokinetics of desirudin following an IV infusion. Administration of ASA had no effect on aPTT and PT values produced by IV infusion of desirudin. Prolonged bleeding times observed in three subjects may not be of clinical significance in these subjects but may be a safety issue in subjects who are susceptible to GI ulceration and bleeding by COX inhibitiors.

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Protein Binding

BPK(F)1994 /030	In vitro binding of desirudin to human serum proteins was investigated by using various methods: equilibrium dialysis, ultrafiltration, ultracentrifug-ation, adsorption on charcoal	**Analytical method** [redacted] **Protein binding** *Equilibrium dialysis* No result were obtained due to the inability of desirudin to pass freely through the membranes *Ultrafiltration* The apparent free fraction was - 15% in plasma - 28% in albumin - 68% in alpha-1-acid glycoprotein - 17% in gamma globulins It ranged from [redacted] for desirudin/thrombin ratio from 13 to 0.64 *Adsorption on charcoal* The apparent free fraction was: - 49% and 75% at 25 nM and >500 nM, resp. - 78% in plasma - 85% in albumin - 92% and 94% in AAG & GG, resp It ranged form [redacted] for desirudin/thrombin ratio from 5 to 0.5	Results of these experiments were difficult to interpret and did not give a definite answer to the question to what extent desirudin binds to serum proteins. Desirudin did not pass freely through the membranes during equilibrium dialysis. It might have an apparent mol. wt. Greater than that based on primary structure. Multimeric aggregates might explain its anomalous behavior. With high mol. wt. compounds, underevaluation of the free drug concentration in the ultrafiltrate is possible due to sieve effect. A preliminary experiment showed that a soln. of desirudin in phosphate buffer was no longer homogenous after ultracentrifugation of desirudin. There this procedure is not appropriate to determine the binding of desirudin to proteins. The optimum conc. of charcoal was difficult to determine in absence of protein (the adsorbed fraction always increased with increasing charcoal conc.). In addition, thrombin did not allow to obtain an accurate control of adsorption on charcoal.

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CRB R43/1993 (RH/E10, RH/E15, US01)	Thrombin-hirudin complex (THC) plasma concentrations after IV and SC administration to healthy young or elderly subjects and patients	**Analytical method** ELISA method does not cross-react with free desirudin or free thrombin. Monoclonal antibody recognizes an epitope expressed selectively upon binding of desirudin to thrombin Precision: [redacted] Accuracy: [redacted] LOQ: [redacted] nmol/L (CV = 18%) **Pharmacokinetics**			AUC of THC represented only around 1% on average of AUC of free desirudin. Thus, THC formation probably contributes only negligibly to the clearance of desirudin.
		Young subjects	0.5 mg/kg IV	0.5 mg/kg SC	
		C_{max} (nmol/L)	[redacted]		
		T_{max} (hr)	1.25	1.75	
		AUC (nmol.h/L)	5.1	6.7	
		AUC ratio (%) (TCA:free desirudin)	0.82	1.11%	
		Elderly subjects	0.3 mg/kg SC		
		C_{max} (nmol/L)	0.41		
		T_{max} (hr)	2.0		
		AUC (nmol.h/L)	4.5		
		AUC ratio (%) (TCA:free desirudin)	1.02		
		Patients (IV infusion over 6 hr)			
			0.02 mg/kg/h	0.3 mg/kg/h	
		C_{max} (nmol/L)	[redacted]		
		T_{max} (hr)	6.0	6.13	
		AUC (nmol.h/L)	6.5	10.3	
		AUC ratio (%) (TCA:free desirudin)	3.3	0.48	

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Metabolism & Elimination

DM(EU) 9/1994	The renal elimination, biotransformation and uptake and the urinary excretion of desirudin were studied in the isolated perfused rat kidney model	**Analytical method** HPLC ***Ex vivo* data** Desirudin in perfusate decreased with apparent half-life of 1.7 – 2.5 hr. The renal clearance was about ½ glomerular filtration rate and ~3-times lower than the total systemic clearance in rat *in vivo*. No unchanged parent compd. was excreted in the urine. Metabolites, hir(I-50) and hir(I-52) accounted for 16-22% after the lower and 33-41% after the higher dose. Part of the dose administered was taken up into the kidneys as demonstrated by immunocyto chemical staining	The results suggest that desirudin is eliminated and metabolized largely in the kidney. The sole presence of unchanged desirudin in the perfusate, and the sole presence of two metabolites in urine demonstrated that degradation of desirudin did not occur within the perfused vascular system of the kidney but after glomerular filtration in the tubular system. Immunocytochemical staining was most intense in the epithelial cells around the proximal tubules and brush border, indicating uptake by endocytosis. Although there was good qualitative agreement between data obtained from in vivo studies and isolated perfusion study, the renal clearance value was significantly lower than that predicted from in vivo results.
DMET(EU) 3/1995	The in vitro biotransformation of desirudin in homogenate fraction(S3) of kidney and liver of the male rat, the dog, the baboon and man (only liver) were investigated.	**Analytical method** HPLC, ELISA, ***In vitro* data** Rat liver S3 fraction degraded about half of the added desirudin with 24 hrs, whereas in dog, baboon, and man degradation was marginal. The main metabolites in rat liver were hir(I-49) and hir(I-62) and the tail fragments hir(53-65) and hir(54-65) Rat kidney S3 fraction degraded desirudin within 2 hrs at pH 7.4, whereas practically no biotrans-formation was observed in dog and baboon. The main metabolites were hir(I-50), hir(I-52), hir(I-56) and hir(I-61) and the tail fragments hir(53-65) and hir(55-65)	At pH 4.0, which is suitable condition for lysosomal enzymes, desirudin was rapidly degraded by kidney homogenate fractions of rat, dog and baboon. These results indicate that while only rats seem to possess endopeptidases capable of degrading desirudin in the renal proximal tubule, in all animal species the intrinsic capability of lysosomal enzymes for degrading reabsorbed desirudin is large.
CRB R 39/1993	Urinary excretion was investigated in five studies using IV (bolus or Infusion) or SC route with IV doses ranging from 0.02 to 1.5 mg/kg and the SC doses ranging from 0.3 to 0.5 mg/kg.	**Analytical method** ELISA **Urinary excretion** IV: 50% of the dose was recovered in the urine. Most of the excretion occurred within 2 hr post-dosing SC: 37% of the dose was recovered in the urine. Excretion was almost complete after 8 – 10 hr post-dosing. Elderly / Young Creatinine clearance (ml/min): 52 ± 10 / 122 ± 21 Renal clearance (ml/min): 42 ± 14 / 58 ± 14	Only 37% was recovered in urine after SC administration compared to 50% using the IV route. This difference may be explained by overloading of the tubular reabsorption pathway with the IV route. Assuming desirudin is taken up by the kidney tubule and are irreversibly lost, the GFR is a measure of true clearance. Then the difference between total plasma clearance and creatinine clearance will represent non-renal clearance of desirudin. Non-renal clearance would then account for ~53% in elderly compared to ~20% in young population. PK-PD relationship was not different in elderly compared to young healthy volunteers.

Report DM 11/1993 **Metabolism and renal excretion of CGP 39 393 (r-hirudin) in volunteers following intravenous infusion. Protocol RH/ET4. Vol. 1.43, p 6-14-127.**

Study design: Urine samples were collected from six out of 12 adult healthy male volunteers during a PK/PD interaction study between CGP 39 393 and 300 mg acetyl salicylic acid.

Treatment: 0.3 mg/kg/hr CGP 39 393 was administered as IV infusion for 6 hr as a solution in sterile 0.9% saline.

Sample collection: Urine was collected quantitatively in four fractions for 36 hr and stored frozen at –20°C until analysis.

Analytical method: For analysis by ELISA the 0 – 24 hr fractions were used.
For HPLC analysis, only 0 – 6 hr samples were used.
For detection of CGP 39 393, reference compounds and metabolites, the UV absorption at [redacted] was monitored with a UV-detector.
For [redacted] only 0 – 6 hr samples were used.

Results & Discussion: CGP 39 393 and hir(I-63) were detected in direct urine analysis using [redacted] CGP 39 393, hir(I-63), and hir(1-64) were unambiguously identified by [redacted] after separation from urine by HPLC. No other relevant metabolites were identified in the urine. The stepwise degradation of the C-terminus of r-hirudin catalyzed by carboxypeptidase was the only metabolic process observed.

Fragments of CGP 39 393, which were prepared as potential metabolites by degradation of the C-terminus using peptidases and which retained at the amino acid sequence I-49, were detected by the established ELISA assay and by HPLC with UV detection. ELISA assay however does not discriminate between native CGP 39 393 and metabolites of CGP 39 393 with partially degraded C-termini. All the CGP 39 393 fragments containing the amino acid core sequence I-49, gave a positive response in the ELISA.

The excretion of CGP 39 393 and its metabolites accounted for about 46% of the dose as estimated by ELISA. About 37% of the dose was excreted unchanged. The fate of the remainder of the dose (54%) was not elucidated.

As stated in the literature, peptides and low molecular weight proteins are generally extensively filtered by the glomeruli and then reabsorbed at the proximal tubular level. After this tubular reabsorption, the peptides and proteins are degraded in lysosomes to individual amino acids, which are then recycles to blood (Adv Drug Deli Rev 1990;4:149-69 & In: Seldin DW Giebisch G, editors. The kidney: physiology and pathophysiology. New York: Raven Press, 1992; 3005-35)

Special Population

Renal Impairment

US 08	Two-center, open-label, parallel group administration of single 30 min IV infusion of desirudin at the doses of 0.5, 0.5, 0.25, and 0.125 mg/kg in normal subjects (n=8), in subjects with mild (n=4), moderate (n=5), and severe (n=6) renal insufficiency, respectively.	**Analytical method** ELISA in plasma: Accuracy: [redacted] Precision: [redacted] LOQ: [redacted] nmol/L ELISA in urine: Accuracy: [redacted] Precision: [redacted] LOQ: [redacted] **Pharmacokinetics**					Close correlation between total plasma clearance and creatinine clearance was observed indicating kidney as the predominant route of elimination. Mean area under the plasma concentration –time curve increased by a factor of 1.15, 2.83, and 7.0 for subjects with mild, moderate, and severe renal failure, respectively, compared with healthy subjects. It appears recommended dose reductions in renal failure patients were based on changes in pharmacodynamic measures rather than the pharmacokinetics parameters which may not be considered as reliable due to the non-specific assay procedure. However, the sponsor should have considered $AUC_{0\text{-}60hr}$ values in moderate and severe renal failure patients rather than $AUC_{0\text{-}36hr}$ values. Based on the corrected data (to 1 mg/kg) 9-fold reduction in dose should be recommended in severe renal failure and 3-fold reduction in moderate renal failure patients.
			Normal	Mild	Moderate	Severe	
		C_{max} (nmol/l)	[redacted]				
		(nmol/L)/(mg/kg)	863	999	1400	1310	
		t_{max} (hr)	0.5	0.5	0.5	0.5	
		AUC (nmol.hr/L)	596	685	836	1010	
		(nmol.hr/L)/(mg/kg)	1190	1370	3370	8330	
		$t_{1/2}$ (hr)	3.1	2.4	4.0	12.2	
		Median MRT (hr)	1.9	2.5	4.1	10.5	
		CL (ml/min)	165	129	51.2	19.3	
		CL_{renal} (ml/min)	97.8	72.2	29.0	10.5	
		Pharmacodynamics					
		$aPTT_{max}$ (× baseline)	4.3	4.5	4.1	3.9	
		aPTT $AUC_{0\text{-}36hr}$ (× baseline.hr)	48.8	42.1	51.9	71.8	
		$AUC_{0\text{-}60hr}$			76.6	105	
		Corrected to 1 mg/kg	97.6	84.1	306.4	840	

Japanese

CRB R13/1993	Pharmacokinetic study was conducted in 15 Japanese healthy volunteers randomized in 3 blocks of 5 subjects who received IV bolus of 0.02, 0.04, or 0.1 mg/kg, respectively.	**Analytical method** ELISA: LOQ: [redacted] nmol/L Precision: [redacted] **Pharmacokinetics**				Pharmacokinetic data obtained in healthy Japanese volunteers were in agreement with those obtained in Caucasian healthy volunteers.
		Dose (mg/kg)	Urinary Excretion (% of dose)	Renal CL ml/min	Total CL (ml/min)	
		0.02	52 ± 6	97 ± 18	189 ± 35	
		0.04	52 ± 4	92 ± 27	180 ± 54	
		0.10	48 ± 10	87 ± 22	182 ± 27	

Elderly

UK R2/1992 CRB R12/1993 (RH/E15)	Open PK-PD study in 12 healthy elderly volunteers after a single SC dose of 0.3 mg/kg	**Analytical method** ELISA: LOQ: [redacted] nmol/L LOD: 0.2 nmol/L ELISA and TCA values were is close agreement between 10 – 70 nmol/L. AUC and C_{max} were greater for TCA and T_{max} was reduced when compared with ELISA values. **Pharmacokinetics** Median T_{max} (hr): Elderly 2.5 (1.5 – 4.0), Young 1.75 Mean C_{max} (nmol/L): Elderly 59.6 ± 10.9, Young 54.6 ± 9.3 Mean AUC (nmol.h/L): Elderly 446 ± 70, Young 344 ± 50 Total Cl (ml/min): Elderly 110 ± 19, Young 153 ± 25 $T_{1/2}$ (hr): Elderly 3.01 ± 0.48, Young 2.41 ± 0.36 Renal Cl (ml/min): Elderly 42 ± 14, Young 58 ± 14 Total Urinary excretion (0-24h): Elderly 38.2 ± 9% **Pharmacodynamics** Max aPTT prolongation: Elderly 1.6 – 2.1, Young 1.5 – 1.7 T_{max} for aPTT: Elderly 0.5 – 2.0, Young 0.5 – 1.5 **PK-PD relationship** aPTT values closely paralleled that of circulating desirudin concentrations. The relationship appeared curvilinear with desirudin plateau conc. of 40 nmol/L. aPTT ranged between 35 – 65 sec in this region. Similar relationship was also demonstrated in young volunteers.	AUC, C_{max}, T_{max}, and $T_{1/2}$ values were increased in elderly compared to young volunteers. Total plasma clearance was reduced in elderly compared to young volunteers. These young volunteers were not part of the same study, but received the same dose (0.3 mg/kg) in a separate study (RH/ET10). There was a tendency for plasma clearance to decrease in parallel with decreasing creatinine clearance. Assuming desirudin is taken up by the kidney tubule and are irreversibly lost, the GFR is a measure of true clearance. Then the difference between total plasma clearance (110 ml/min) and creatinine clearance (52 ml/min) will represent non-renal clearance of desirudin. In this group of subjects non-renal clearance accounts for ~53%. PK-PD relationship was not different in elderly compared to young healthy volunteers.

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Bioequivalence

RH/E36	Open-label, randomized, cross-over, single-center, single-dose bioequivalence trial in 12 healthy male volunteers who received SC doses of 15 mg desirudin as the F4 (new) and F1 (clinical trial) formulations	**Analytical method** ELISA LOQ [redacted] nmol/L Precision: [redacted] Accuracy [redacted] **Pharmacokinetics** F1 vs F4 C_{max} (nmol/L): 38.5 ± 9.1 / 35.7 ± 6.1 T_{max} (hr): 2.0 / 2.5 AUC_{0-24h} (nmol.h/L): 209 ± 25 / 204 ± 29 $AUC_{0-\infty}$ (nmol/L): 211 ± 27 / 204 ± 30 $T_{1/2}$ (hr): 1.9 / 2.1 $AUC_{0-\infty}$ Ratio (F4/F1) = 0.967 90% C.I.: 0.93 – 1.07 C_{max} Ratio (F4/F1) = 0.927 90% C.I.: 0.85 – 1.04 **Pharmacodynamics** Ratio of AUC_{0-24h} for aPTT (F4/F1) = 0.9786 90% C.I.: 0.9499 – 1.0081	In the new formulation F4, the only change, [redacted] was replaced by $MgCl_2$, whereas the composition and volume of the solvent used for reconstitution remained the same. Similar plasma levels, pharmacokinetic parameters and pharmacodynamic effects were observed with F1 and F4 formulations [Figure 19]. The conc.-response relationship were also investigated using NONMEM analysis and found not different for formulation F4 compared with formulation F1.

Miscellaneous

BPK(CH) 1995/042	Plasma concentration-time data from two studies in man were compared with data animal data	**Pharmacokinetics** **Man / Dog / Monkey / Rat** AUC (nmol.h/L)/(mg/kg): 1176 / 716 / 553 / 203 CL (ml/min/kg): 2.0 / 3.3 / 4.3 / 11.8 MRT (hr): 1.55 / 0.78 / 0.49 Vss (L/kg): 0.19 / 0.28 / 0.35	The rate of elimination of desirudin from systemic circulation was inversely related to the body size and consequently AUC increased with increased body size

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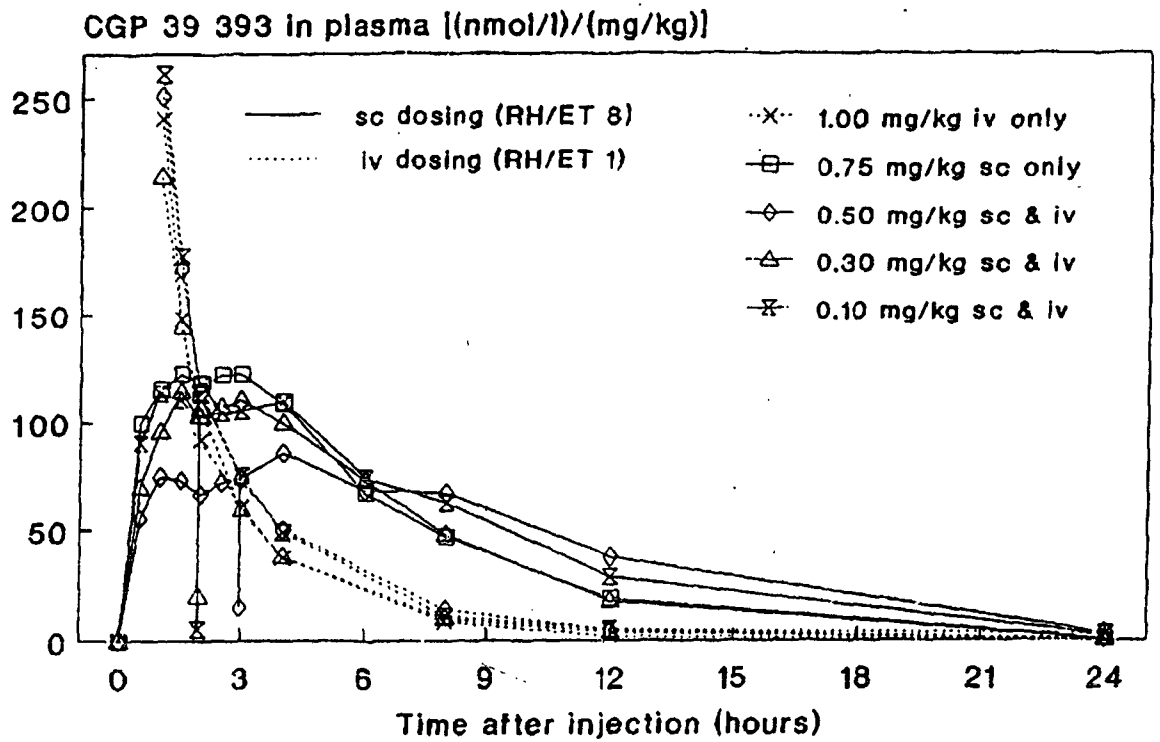
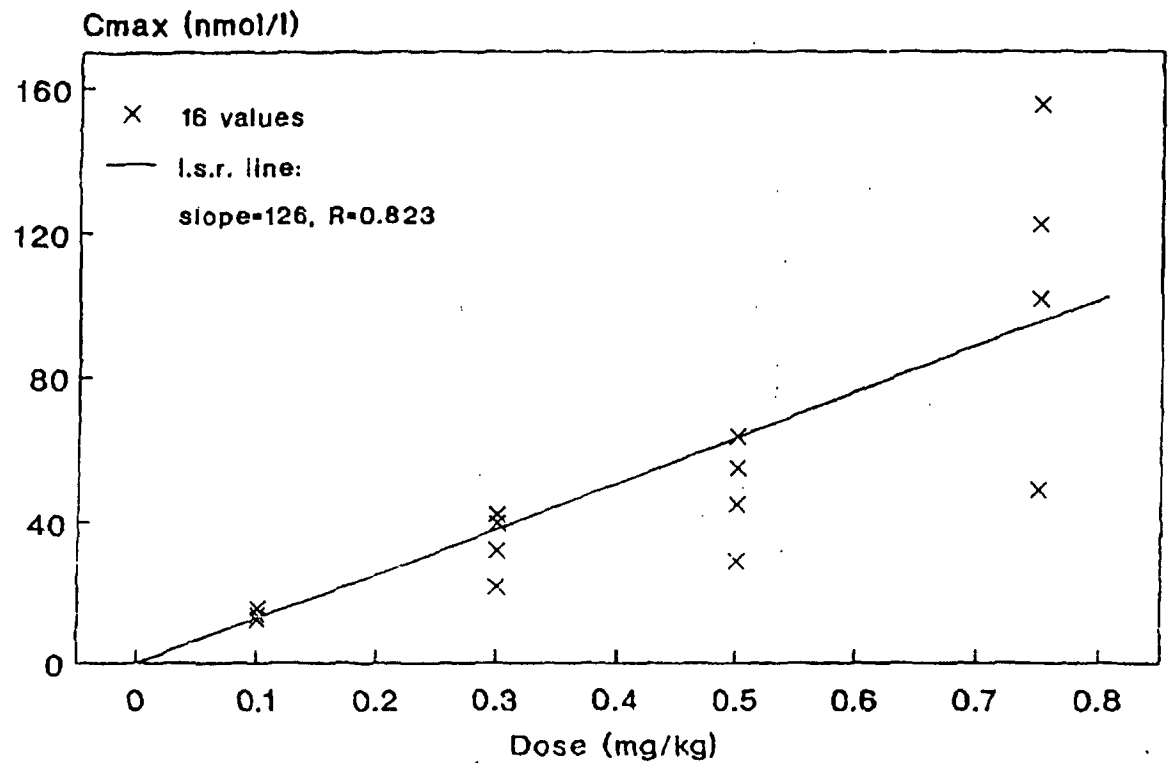
Figure 1

Dose-Normalized Mean Concentration-Time Curves for iv (N=8) and sc (N=4) Dosing



CGP 39 393. Protocol RH/ET 8. Intersections of corresponding curves marked by vertical lines.

Figure 2



l.s.r.: linear least squares regression.
Concentrations measured by ELISA.

Figure 3

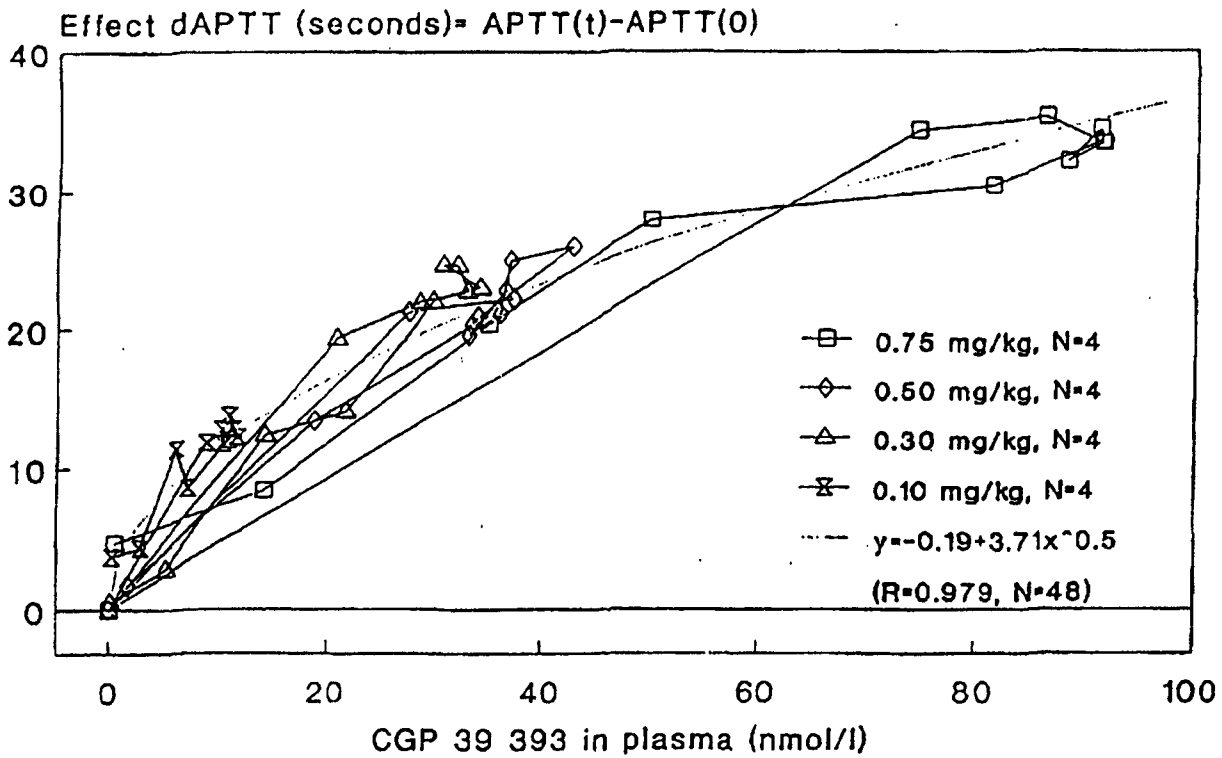
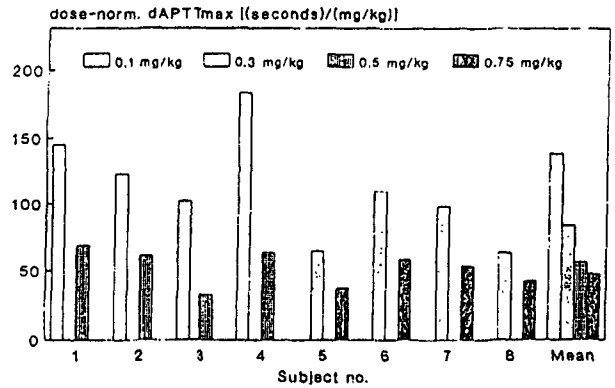
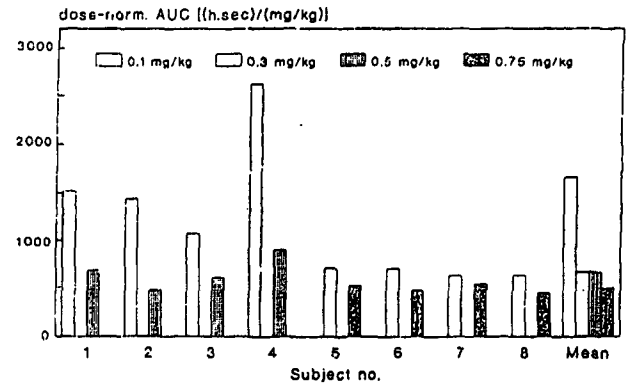
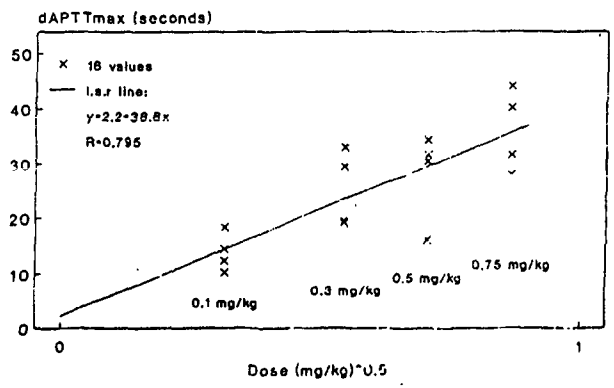

Effect dAPTT (seconds)= APTT(t)-APTT(0)
40
30
20
10
0
0
20
40
60
80
100
CGP 39 393 in plasma (nmol/l)
0.75 mg/kg, N=4
0.50 mg/kg, N=4
0.30 mg/kg, N=4
0.10 mg/kg, N=4
y=-0.19+3.71x^0.5
(R=0.979, N=48)

Figure 4


dose-norm. dAPTTmax [(seconds)/(mg/kg)]
0.1 mg/kg
0.3 mg/kg
0.5 mg/kg
0.75 mg/kg
200
150
100
50
0
1
2
3
4
5
6
7
8
Mean
Subject no.


dose-norm. AUC [(h.sec)/(mg/kg)]
0.1 mg/kg
0.3 mg/kg
0.5 mg/kg
0.75 mg/kg
3000
2000
1000
0
1
2
3
4
5
6
7
8
Mean
Subject no.


dAPTTmax (seconds)
16 values
l.s.r. line:
y=2.2+38.8x
R=0.795
50
40
30
20
10
0
0.1 mg/kg
0.3 mg/kg
0.5 mg/kg
0.75 mg/kg
0
1
Dose (mg/kg)^0.5

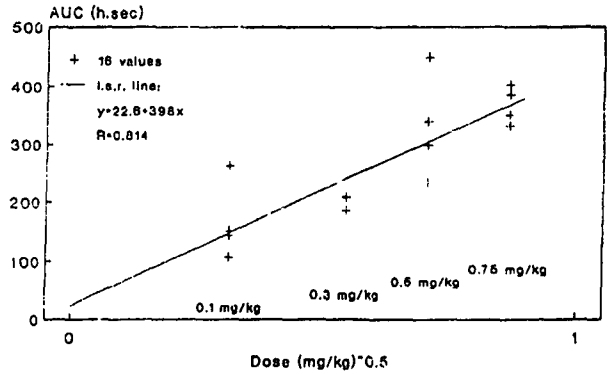
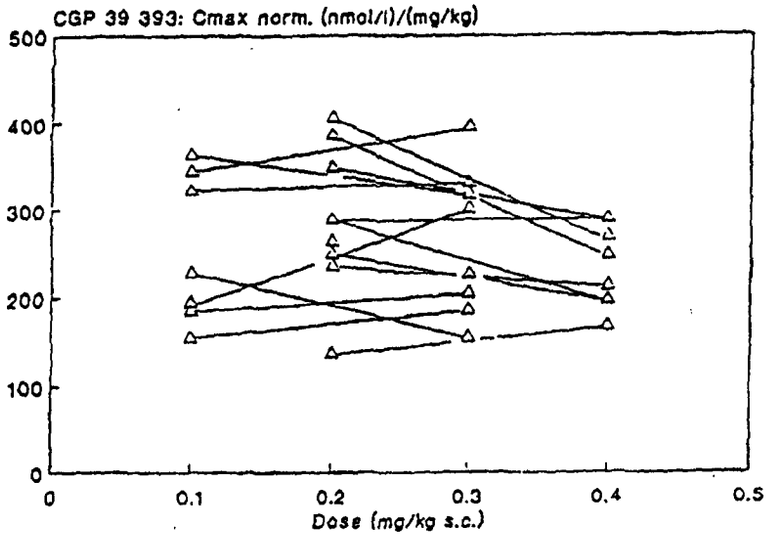

AUC (h.sec)
16 values
l.s.r. line:
y=22.6+398x
R=0.814
500
400
300
200
100
0
0.1 mg/kg
0.3 mg/kg
0.5 mg/kg
0.75 mg/kg
0
1
Dose (mg/kg)^0.5

Figure 5



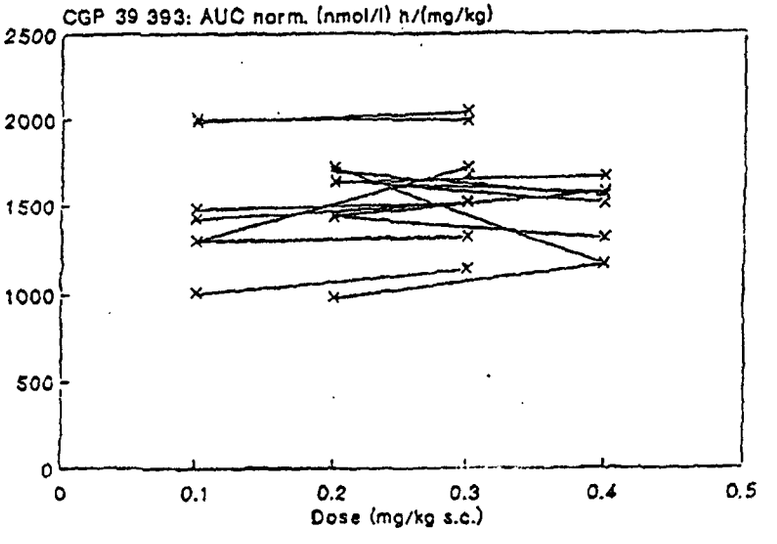


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Figure 6

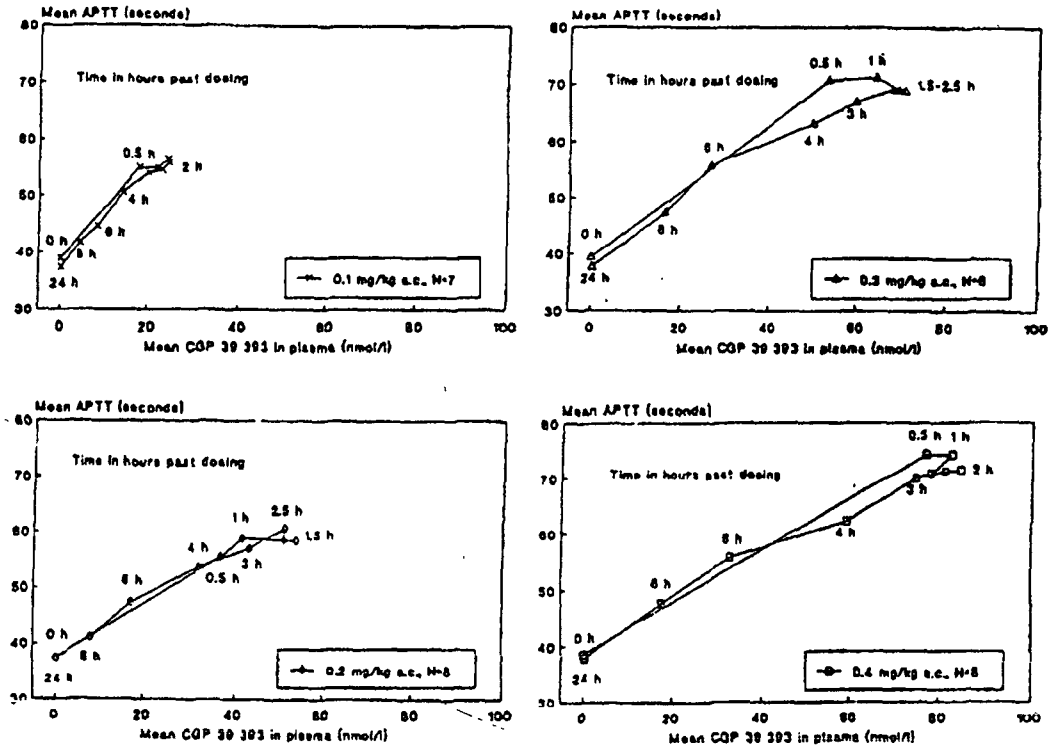

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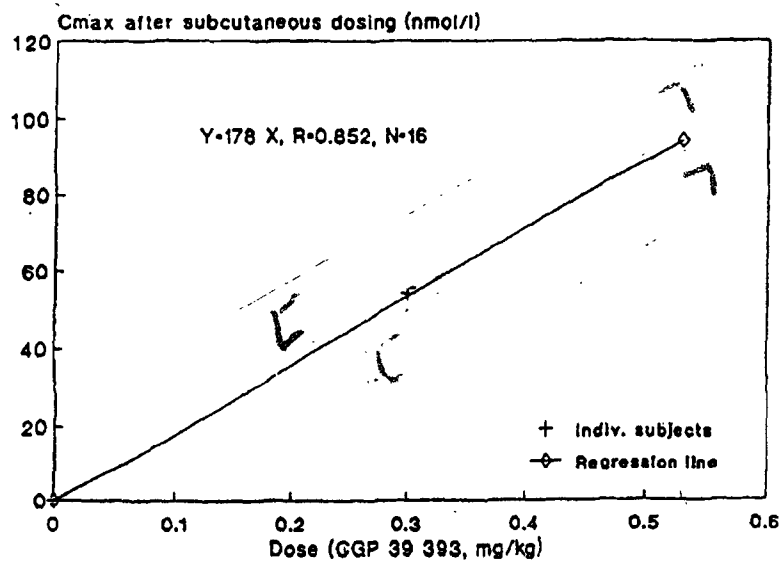
Figure 7



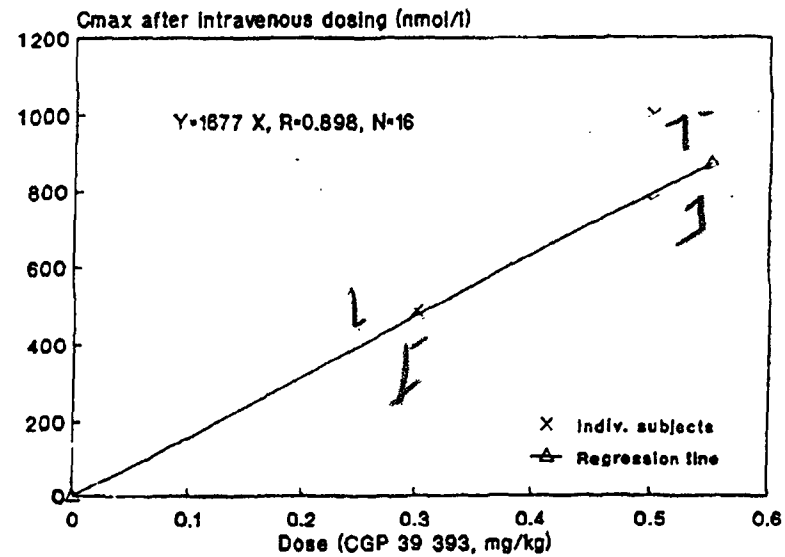


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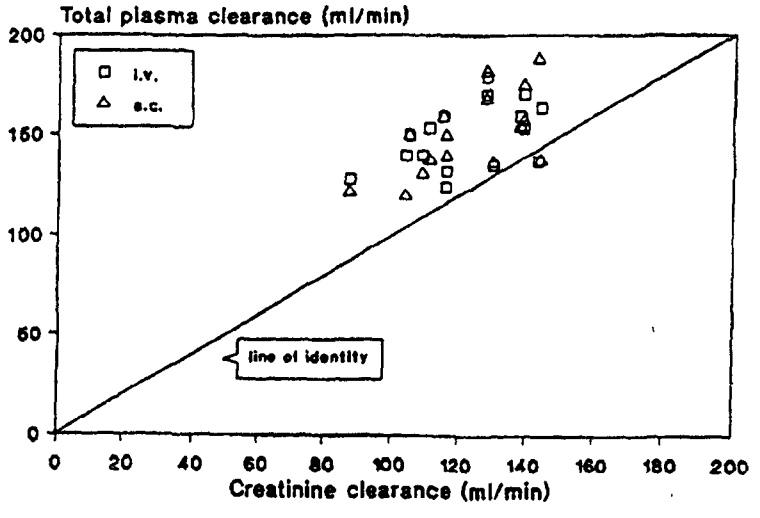
Figure 8



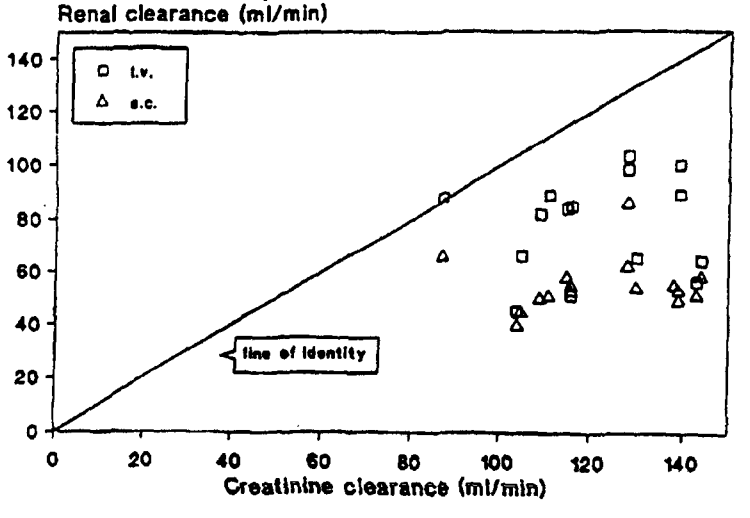


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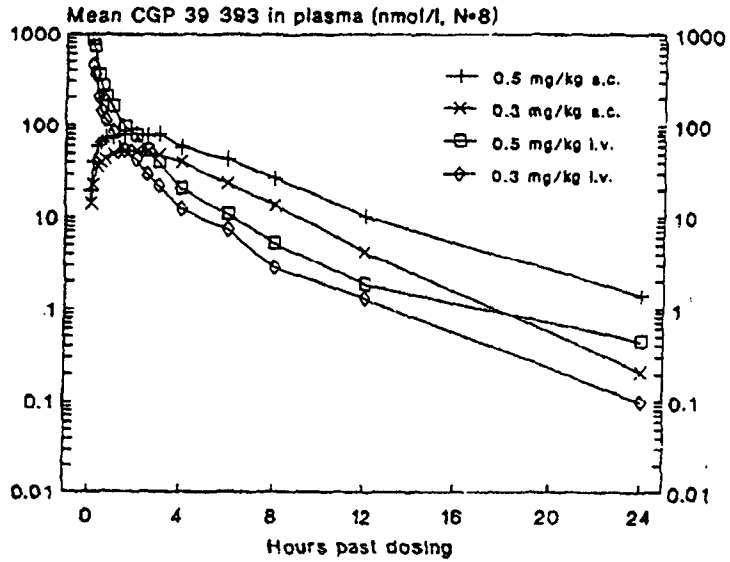
Figure 9



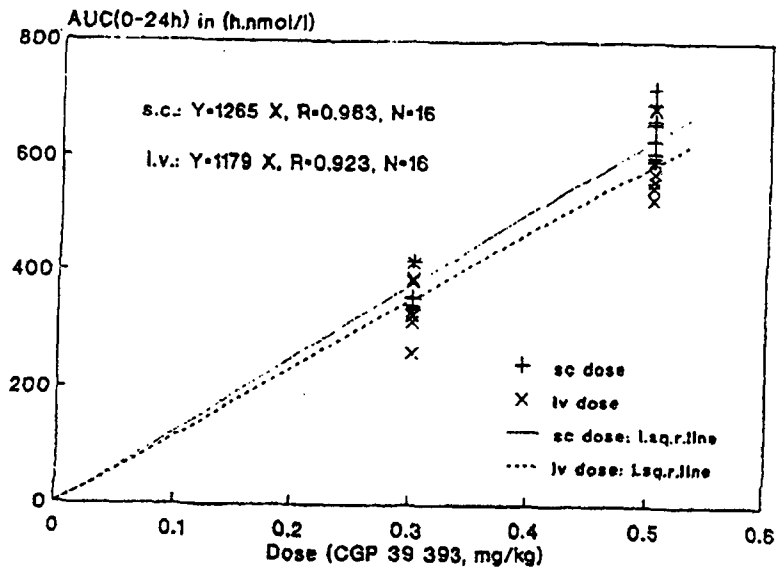


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Figure 10

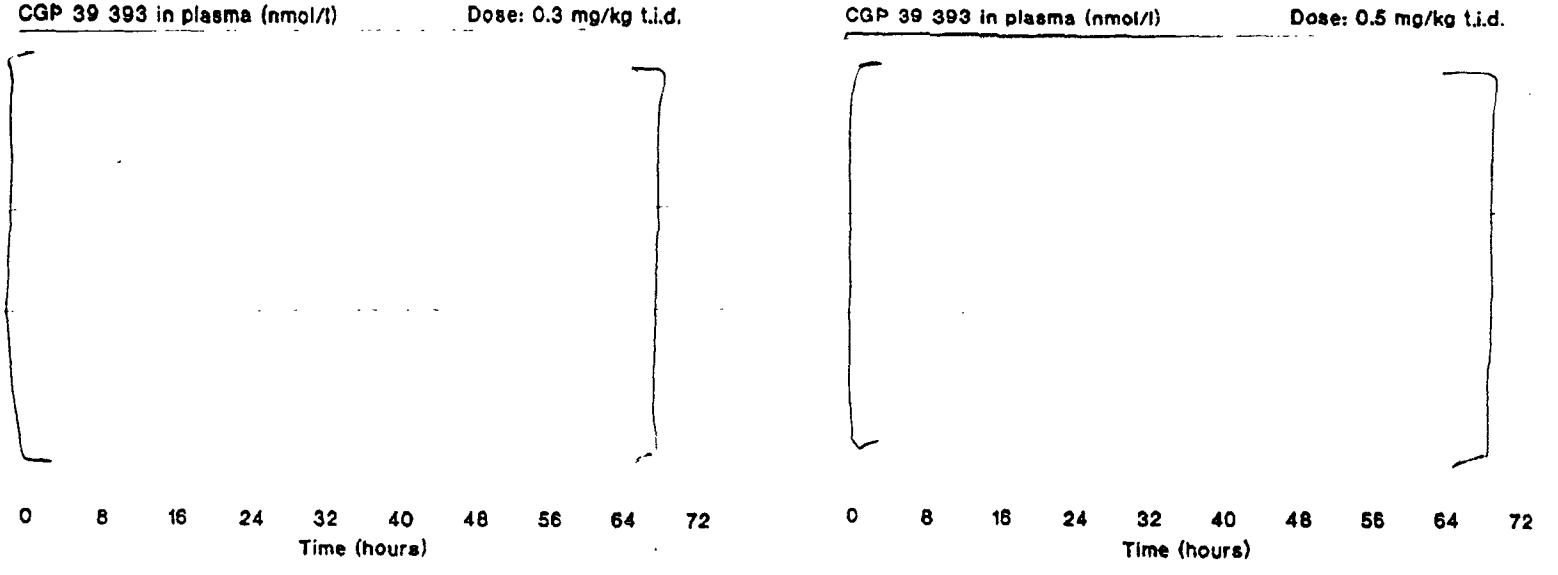

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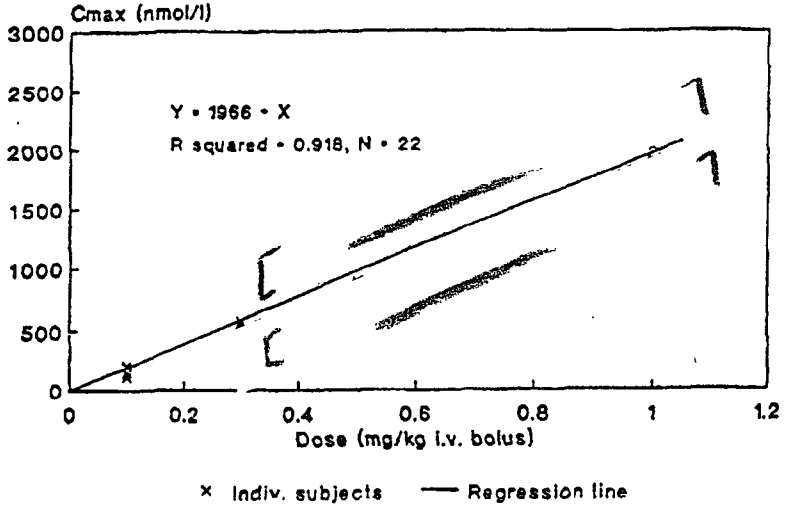
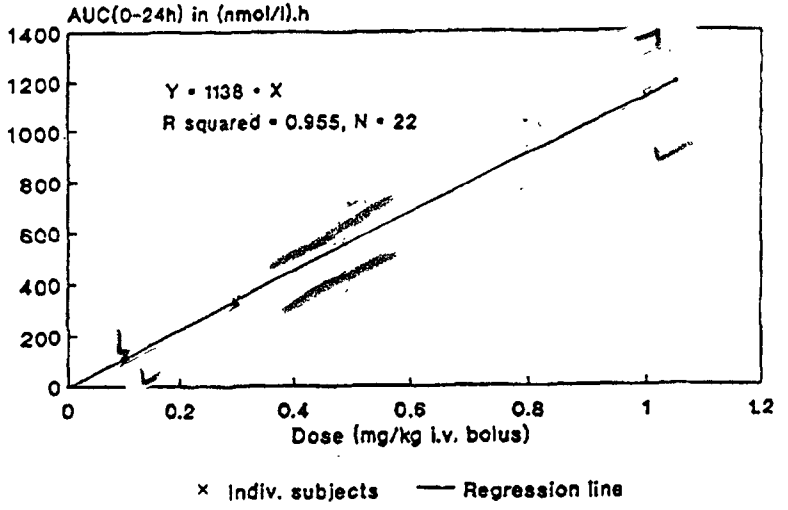
Figure 11





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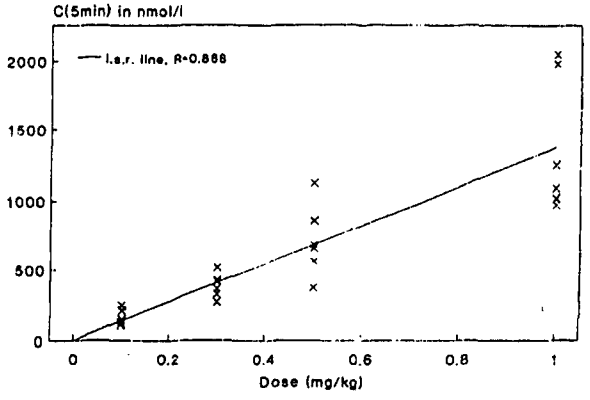
ON ORIGINAL

Figure 12



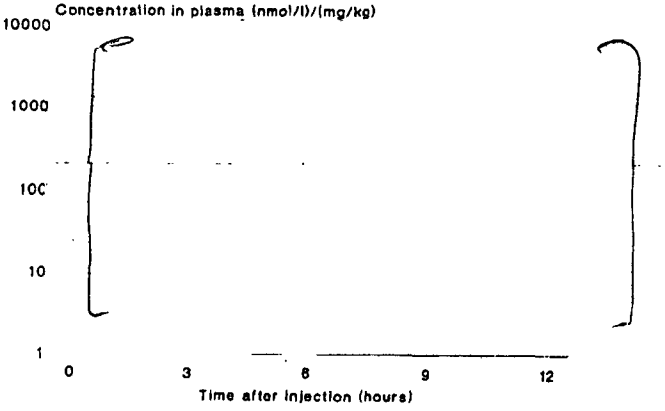


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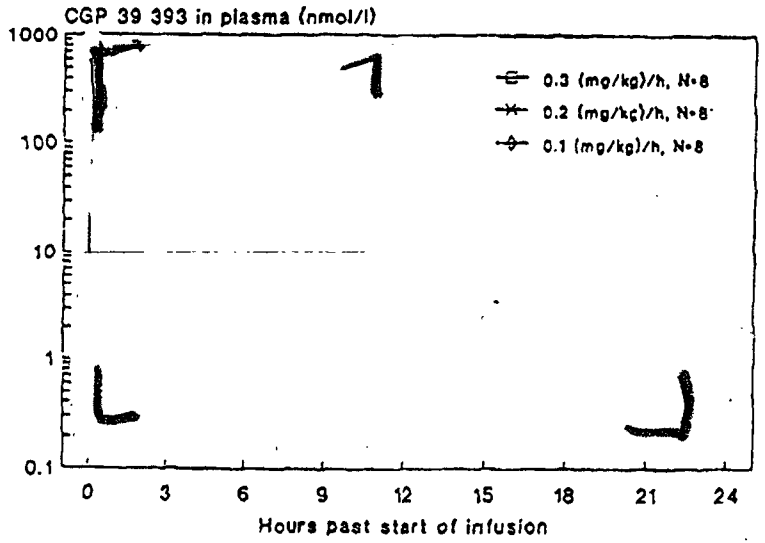
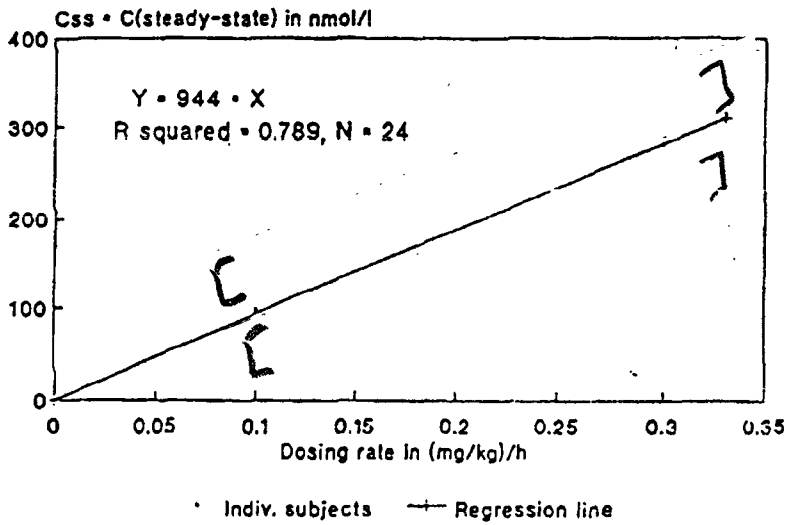
Figure 13


CGP 39 393 in plasma (nmol/l)
1000
100
10
1
0.1
0 3 6 9 12 15 18 21 24
Hours past start of infusion
0.3 (mg/kg)/h, N=8
0.2 (mg/kg)/h, N=8
0.1 (mg/kg)/h, N=8


Css = C(steady-state) in nmol/l
400
300
200
100
0
Y = 944 * X
R squared = 0.789, N = 24
0 0.05 0.1 0.15 0.2 0.25 0.3 0.35
Dosing rate in (mg/kg)/h
Indiv. subjects
Regression line

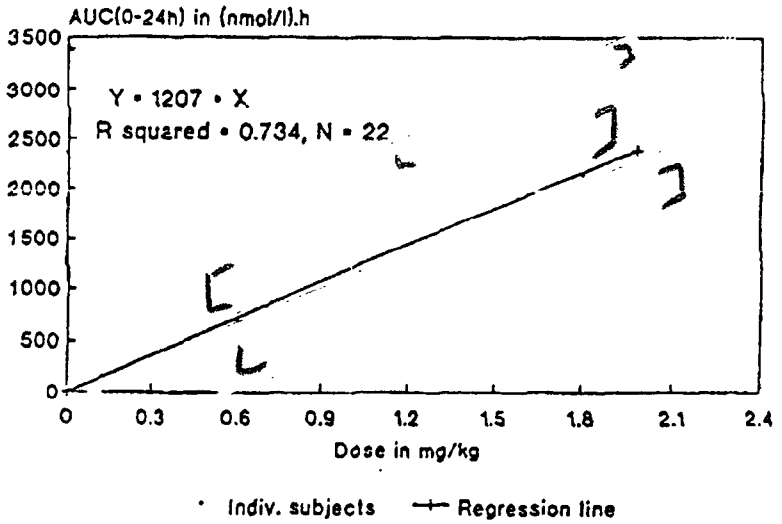

AUC(0-24h) in (nmol/l).h
3500
3000
2500
2000
1500
1000
500
0
Y = 1207 * X
R squared = 0.734, N = 22
0 0.3 0.6 0.9 1.2 1.5 1.8 2.1 2.4
Dose in mg/kg
Indiv. subjects
Regression line

Figure 14

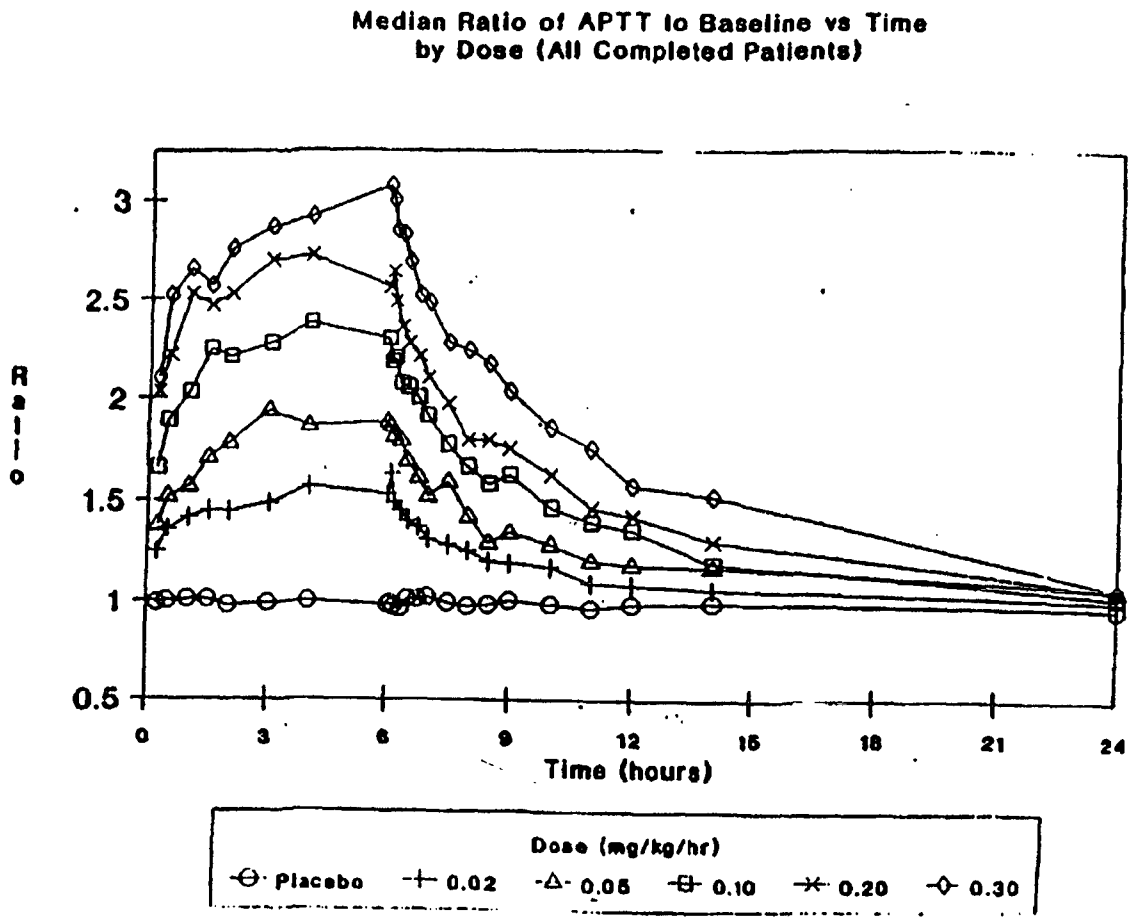
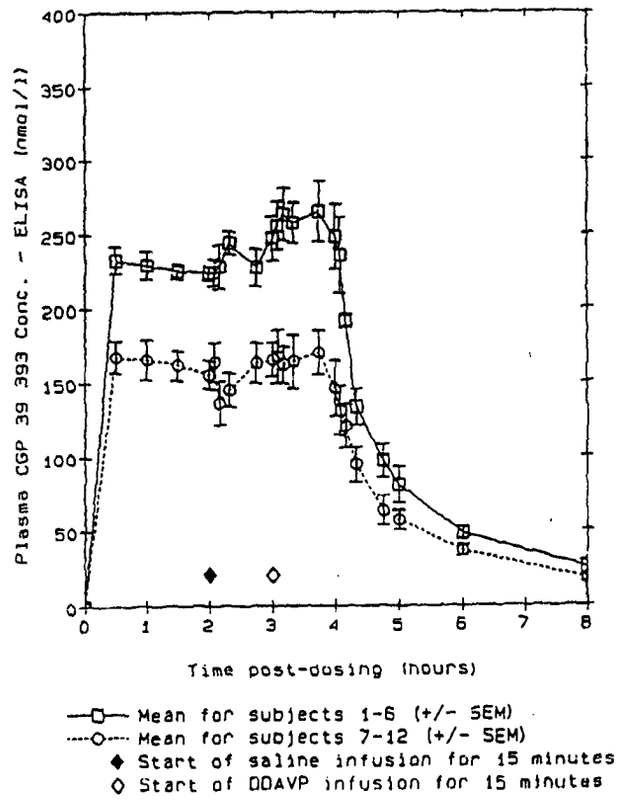

Median Ratio of APTT to Baseline vs Time
by Dose (All Completed Patients)
Ratio
3
2.5
2
1.5
1
0.5
0
3
6
9
12
15
18
21
24
Time (hours)
Dose (mg/kg/hr)
Placebo
0.02
0.05
0.10
0.20
0.30

Figure 15


Plasma CGP 39 393 Conc. - ELISA (nmol/l)
Time post-dosing (hours)
Mean for subjects 1-6 (+/- SEM)
Mean for subjects 7-12 (+/- SEM)
Start of saline infusion for 15 minutes
Start of DDAVP infusion for 15 minutes

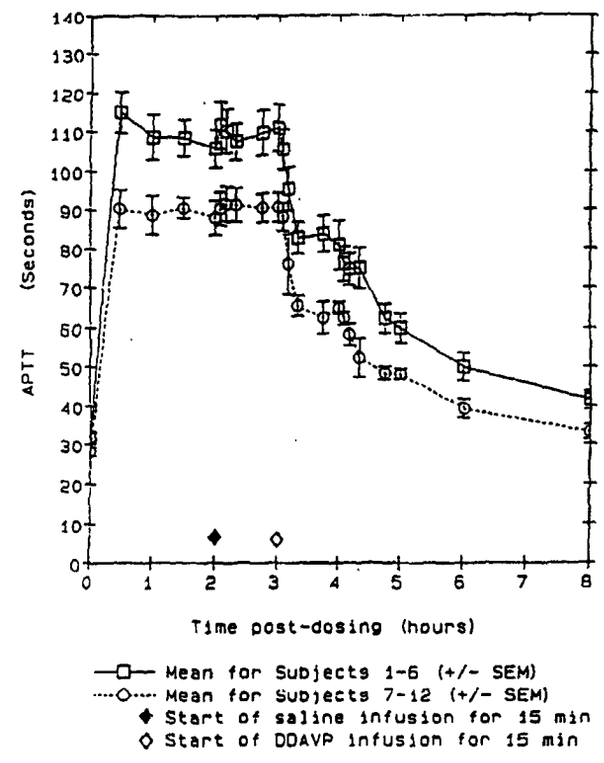
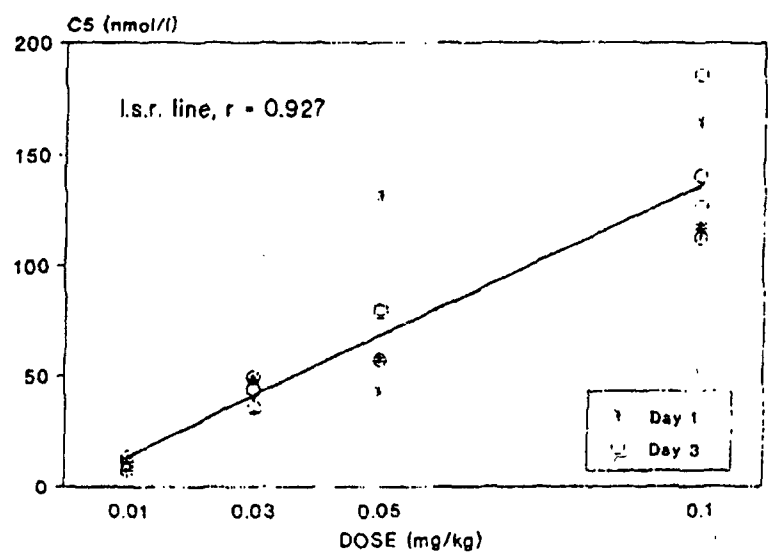

APTT (Seconds)
Time post-dosing (hours)
Mean for Subjects 1-6 (+/- SEM)
Mean for Subjects 7-12 (+/- SEM)
Start of saline infusion for 15 min
Start of DDAVP infusion for 15 min

Figure 16

Day 1 – alone
Day 3 – combination with heparin



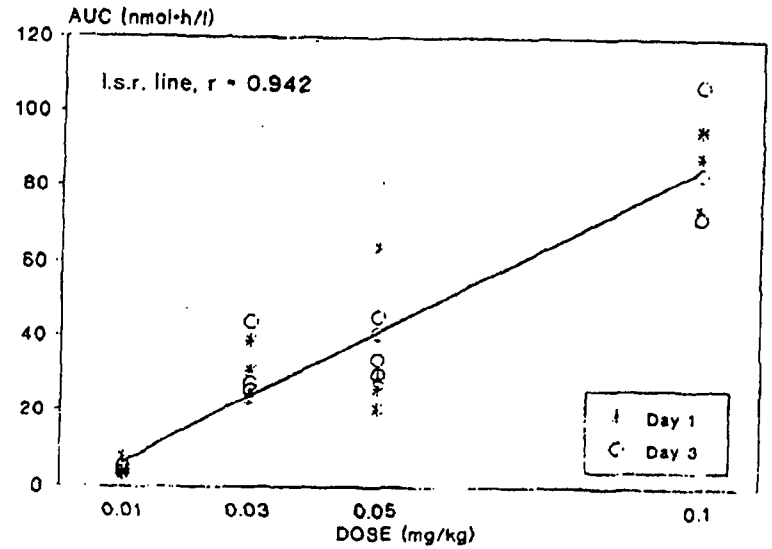


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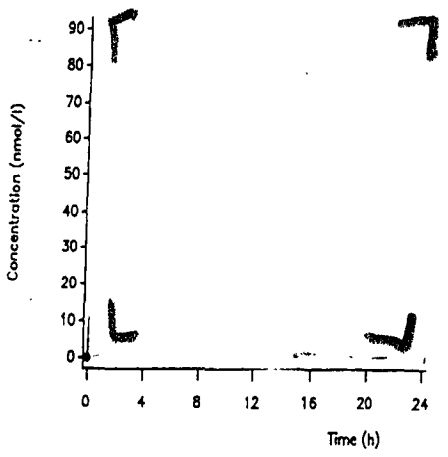
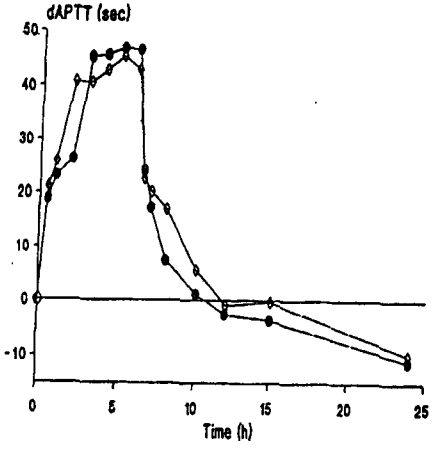
Figure 17


Concentration (nmol/l)
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)


dAPTT (sec)
50
40
30
20
10
0
-10
0
5
10
15
20
25
Time (h)

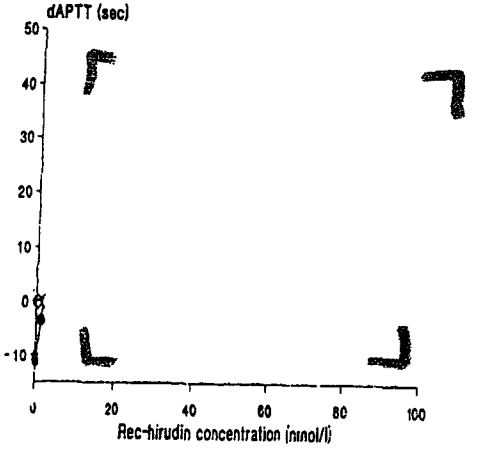

dAPTT (sec)
50
40
30
20
10
0
-10
0
20
40
60
80
100
Rec-hirudin concentration (nmol/l)

Figure 18

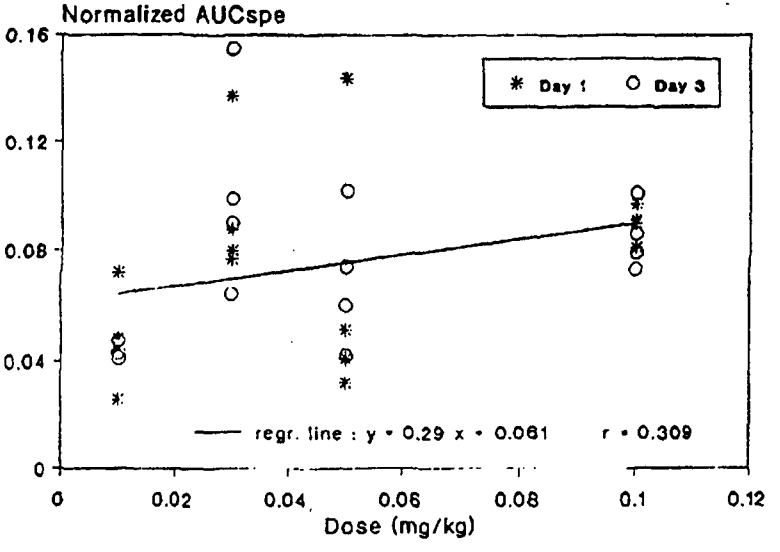


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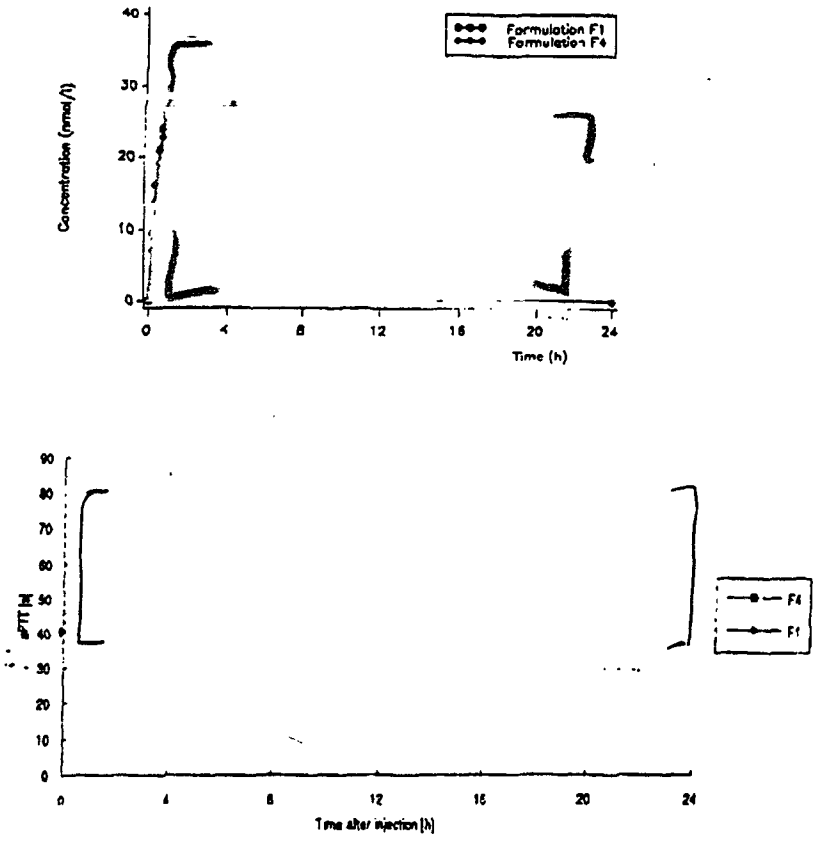
Figure 19


Formulation F1
Formulation F4
Concentration (nmol/l)
Time (h)
F4
F1
Time after injection [h]

Dubeau

AUG 28 1999

New Drug Application

Clinical Pharmacology and Biopharmaceutics Filing Review

NDA:	21-271			
Submission(s):	Type:	Suppl.: 000	Letter Date: 6/28/00	Date Received: 6/28/00
Reviewer:	Sandip K. Roy, Ph.D.			
Clinical Division:	Division of Gastrointestinal and Coagulation Drug Products, HFD-180			
Drug:				
Generic Name:	Desirudin			
Other Name(s):	RPR205511, CGP39393			
Trade Name:	[redacted]			
Molecular Weight:	6963.52			
Molecular Formula:	$C_{287}H_{440}N_{80}O_{110}S_6$			
Structural Formula:				
Relevant IND(s)/NDA(s):	IND 34,046			
Drug Class:	Anticoagulant			
Dosage Form:	Single dose (15 mg) lyophilized powder			
Route of Administration:	Subcutaneous injection			
Dosing Regimen:	15 mg every 12 hrs administered by subcutaneous injection			
Sponsor:	Aventis Pharmaceuticals Products Inc., Collegeville, PA			
Proposed Indication:	Prevention of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery			

Items included in NDA (CTD)	**Yes**	**No**	**Request**
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies	X		
Mass Balance Study		X	
BA Studies	X		
Absolute BA	X		
Relative BA		X	
BE Studies	X		
Average BE	X		
Population BE		X	
Individual BE		X	
Food-Drug Interaction		X	
Dissolution Tests (*In Vitro-In Vivo* Comparison Studies)		X	
Studies Using Human Biomaterials	X		
Plasma Protein Binding Studies	X		
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc	X		
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies	X		
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose	X		

PK, and Initial Safety and Tolerability in Patient Volunteers	X		
Single Dose	X		
Multiple Dose	X		
Dose Proportionality	X		
Single Dose	X		
Multiple Dose	X		
PK in Population Subsets to Evaluate Effects of Intrinsic Factors	X		
Ethnicity	X		
Gender	X		
Pediatrics		X	
Geriatrics	X		
Renal Impairment	X		
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors	X		
Drug-Drug Interaction: Effects on Primary Drug	X		
Drug-Drug Interaction: Effects of Primary Drug	X		
Population PK studies	X		
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers	X		
PK/PD studies in patients	X		
Individual Datasets for all PK and PK/PD studies in electronic format		X	
Other		X	
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

List of OCPB related studies & reports submitted under this NDA:

Summary of Human Pharmacology and Biopharmaceutics. Vol. 1.1, p 3-1-193.

Human Pharmacology Summary. Vol. 1.30, p 6-1-1.

Intravenous

Pharmacokinetics:

An open, comparative, single-dose trial (two intravenous bolus injections) with rec-hirudin in healthy volunteers never previously exposed to hirudin. Protocol RH/ET7. Vol. 1.30, p 6-1-404.

CGP 39393 (r-Hirudin): Plasma concentrations in healthy volunteers after single i.v. bolus injections of 0.1, 0.3, 0.5 and 1.0 mg/kg. Report B 82/1989. Vol. 1.31, p 6-2-212.

An open, comparative, single-dose trial (two intravenous infusions) with rec-hirudin in healthy volunteers never previously exposed to hirudin. Protocol RH/ET2. Vol. 1.31, p 6-2-260.

CGP 39393 (r-Hirudin): Plasma concentrations in healthy volunteers during and after a 6-hour i.v. infusion of 0.1, 0.2 and 0.3 (mg/kg)/h. Report B 76/1989. Vol. 1.32, p 6-3-192.

Single-blind, placebo-controlled, ascending-dose study to evaluate the effects of CGP-39393 given as a 6-hour infusion, on coagulation parameters in patients with stable coronary artery disease. Protocol US 01. Vol. 1.35, p 6-6-1.

An open-label, ascending-dose study to evaluate the effects of CGP-39393, given as an intravenous bolus, alone and in combination with heparin, on coagulation parameters in normal healthy volunteers. Protocol US 03. Vol. 1.41, p 6-12-1.

Pharmacokinetics of rec-hirudin given as intravenous bolus injections of ascending doses, alone and in combination with heparin in normal healthy volunteers. Report R12/1992. Vol. 1.42, p 6-13-182.

CGP 39393: A study to investigate the effects of DDAVP, given as a 15 minute infusion, on the pharmacokinetics and pharmacodynamics of CGP 39393 during a 4 hour intravenous infusion of CGP 39393 in twelve male volunteers. Report UK R3/1991. Vol. 1.43, p 6-14-1.

CGP 39 393 (r-Hirudin): Pharmacokinetics in man and animals. Report BPK(CH) 1995/042. Vol. 1.46, p 6-17-265.

PK/PD Relationship:

CGP 39393 (r-Hirudin): Pharmacokinetic-pharmacodynamic relationship for ir bolus injections of 0.1, 0.3, 0.5 or 1.0 mg/kg in 8 healthy volunteers each. Report B 104/1990. Vol. 1.30, p 6-1-373.

Pharmacokinetic and pharmacodynamic interaction study after an intravenous infusion of Recombinant hirudin (CGP 39393) and single oral doses of acetyl salicylic acid (ASA), in twelve healthy male volunteers. Report UK R5/1990. Vol. 1.39, p 6-10-264.

Double-blind, randomized, placebo-controlled cross-over pharmacokinetic and pharmacodynamic interaction study after co-administration of an intravenous infusion of CGP 39393 (rec-hirudin) and repeated oral doses of piroxicam in twelve healthy male volunteers. Protocol RH/E34. Vol. 1.40, p 6-11-1.

Effect of DDAVP on the pharmacokinetics and pharmacodynamics of rec-hirudin during an intravenous infusion of either 0.3 or 0.2 mg/kg/h in two groups of six healthy male volunteers. Plasma concentrations of rec-hirudin measured by ELISA and comparison with TCA values. Report R43/1991. Vol. 1.43, p 6-14-170.

Special Population:

A comparative evaluation of the pharmacokinetics and pharmacodynamics of CGP 39 393, given intravenously over a period of 30 minutes to subjects with normal renal functions and to subjects with varying degrees of renal insufficiency. Protocol Trial US 08. Vol. 1.46, p 6-17-291.

Subcutaneous

Pharmacokinetics:

An open, comparative, single-dose trial (two subcutaneous applications) with rec-hirudin in healthy volunteers never previously exposed to hirudin. Protocol RH/ET3. Vol. 1.32, p 6-3-283.

CGP 39393 (r-Hirudin): Plasma concentrations in healthy volunteers after two single subcutaneous doses of either 0.1 and 0.3 mg/kg or 0.2 and 0.4 mg/kg. Report B 23/1990. Vol. 1.33, p 6-4-241.

Single dose comparison of one subcutaneous and one intravenous administration of recombinant hirudin (CGP 39393), at two dose levels, in healthy volunteers never previously exposed to hirudin. Report UK R6/1989. Vol. 1.33, p 6-4-302.

CGP 39393 (r-Hirudin): Pharmacokinetics of repeated subcutaneous administrations at 2 dose levels (0.3 or 0.5 mg/kg t.i.d.) for 3 days given to 8 healthy volunteers each. Report B 2/1992. Vol. 1.33, p 6-4-345.

An open, comparative, multiple-dose trial (repeated subcutaneous applications during six days) with rec-hirudin in healthy volunteers previously or never previously exposed to hirudin. Protocol RH/ET9. Vol. 1.34, p 6-5-1.

An open pilot ascending dose finding trial to assess the safety of four dose levels of CGP 39393 in patients undergoing an elective hip replacement. Report RH/PT 03. Vol. 1.35, p 6-6-337.

A multicenter double-blind randomized heparin controlled dose-finding trial evaluating the efficacy of three CGP 39393 dose levels in patients undergoing an elective total hip replacement. Protocol RH/E23. Vol. 1.37, p 6-8-1.

CGP 39393 (r-hirudin): Pharmacokinetics after single iv bolus injections of 0.1. 0.3, 0.5 or 1.0 mg/kg in 8 healthy volunteers each. Report B 103/1990. Vol. 1.43, p 6-14-269.

CGP 39 393 (r-hirudin): Pharmacokinetics after single sc bolus injections of 0.1, 0.3, or 0.5 or 0.75 mg/kg in four healthy volunteers each. Report B 6/1991. Vol. 1.43, p 6-14-393.

CGP 39 393 (r-hirudin): Plasma concentrations in healthy volunteers after single i.v. and s.c. doses of 0.3 and 0.5 mg/kg. Report B90/1989. Vol. 1.44, p 6-15-1.

Pharmacokinetics of rec-hirudin given as a 6-hour intravenous infusion of ascending doses in patients with stable coronary artery disease. Report CRB R 9/1992, Vol. 1.45, p 6-16-166.

Rec-hirudin plasma concentrations after subcutaneous ascending dose administrations in patients undergoing an elective total hip replacement. Report CRB R 31/1992, Vol. 1.45, p 6-16-216.

CGP 39 393 plasma concentrations in orthopaedic patients undergoing an elective total hip replacement. Report BPK(F) 1994/022, Vol. 1.45, p 6-16-263.

Elimination:

Urinary excretion of rec-hirudin in healthy young volunteers after single intravenous and subcutaneous doses of 0.3 or 0.5 mg/kg. Report CRB R 10/1993. Vol. 1.44, p 6-15-385.

Urinary excretion of rec-hirudin after an intravenous bolus injection of 0.2 or 0.3 mg/kg followed by an intravenous infusion of 0.3 or 0.2 mg/kg/h over 4 h in two groups of six healthy male volunteers. Report CRB R 11/1993. Vol. 1.45, p 6-16-1.

Urinary excretion of rec-hirudin after a single subcutaneous administration of 0.3 mg/kg CGP 39 393 to twelve healthy elderly volunteers. Report CRB R 12/1993, Vol. 1.45, p 6-16-30.

Urinary excretion of rec-hirudin after single intravenous bolus administration of 0.02, 0.04 or 0.1 mg/kg CGP 39 393 to Japanese healthy volunteers. Report CRB R 13/1993, Vol. 1.45, p 6-16-60.

Urinary excretion of rec-hirudin after a 6-hour intravenous infusion of ascending doses in patients with stable coronary artery disease. Report CRB R 14/1993, Vol. 1.45, p 6-16-82.

State of the knowledge on urinary excretion of rec-hirudin (ELISA) after intravenous and subcutaneous administrations to healthy volunteers or patients. Report CRB R 39/1993, Vol. 1.45, p 6-16-107.

Drug-drug Interaction:

Open label single centre trial to investigate the possible interaction between CGP 39393 and warfarin in twelve healthy male volunteers. Protocol RH/E35. Report UK R1/1994. Vol. 1.42, p 6-13-235.

Thrombin-hirudin complex plasma concentrations after intravenous and subcutaneous administration of rec-hirudin to healthy young or elderly subjects and patients. Report CRB R43/1993. Vol. 1.44, p 6-15-28.

Analytical method:

CGP 39393, r-hirudin: An ELISA for recombinant hirudin in plasma and urine. Report B125/1988. Vol. 1.43, p 6-14-87.

Determination of rec-hirudin in plasma and urine by an enzyme-linked immunosorbent assay (ELISA). Report R55/1991. Vol. 1.43, p 6-14-103.

Metabolism and renal excretion of CGP 39393 (r-hirudin) in volunteers follow ng intravenous infusion. Protocol RH/ET4. Report DM 11/1993. Vol. 1.43, p 6-14-127.

A [redacted] ELISA for thrombin-hirudin complex (THC) in human plasma. Report CRB R 40/1993. Vol. 1.43, p 6-14-231.

PK/PD Relationship:

CGP 39393 (r-Hirudin): Pharmacokinetic-pharmacodynamic relationship after single sc bolus injections of 0.1, 0.3, 0.5 or 0.75 mg/kg in four healthy volunteers each. Report B 9/1991. Vol. 1.32, p 6-3-244.

A pharmacokinetic and pharmacodynamic study after a single subcutaneous administration of CGP 39393 (recombinant hirudin) to twelve healthy elderly volunteers. Report UK R2/1992. Vol. 1.39, p 6-10-218.

CGP 39 393 (r-hirudin): Pharmacokinetics and kinetic-dynamic relationship of an iv infusion of 0.2 or 0.3 (mg/kg)/h for 3 days in six healthy volunteers each. Report B 1/1992. Vol. 1.43, p 6-14-339.

Protein Binding Studies:

In vitro binding of CGP 39 393 to human serum proteins. Report BPK(F) 1994/030. Vol. 1.44, p 6-15-86.

In vitro metabolism of CGP 39 393 (r-hirudin) in liver or kidney of rat, dog, baboon and man. Report DMET (EU) 3/1995. Vol. 1.44, p 6-15-322.

Population PK/PD Studies:

Population kinetics and dynamic evaluation of phase I studies: a meta analysis. Vol. 1.45, p 6-16-322.

Population pharmaco-kinetics and pharmaco-dynamic evaluations in patients undergoing an elective total hip replacement. Protocol RH/E23, Vol. 1.45, p 6-16-359.

Bioequivalence:

Single dose, open-label, two-period, randomized cross-over bioequivalence study of the two s.c. CGP 39 393 formulations F1 and F4 in twelve healthy male volunteers. Protocol RH/E 36 (HPH 9407), Vol. 1.46, p 6-17-58.

What are the key questions to be considered during the review of this NDA?

1. What is the dose-systemic exposure relationship for desirudin after administration of a single dose?
2. What is the dose-systemic exposure relationship after administration of multiple doses of desirudin?
3. What are the dose and/or systemic exposure relationships of desirudin to different coagulation parameters (PD)?
4. Are the analytical methods used for assay of desirudin adequately validated?
5. What bioavailability and bioequivalence data are available to assess the quality of the subcutaneous formulation of desirudin?
6. What is the effect of renal impairment on the pharmacokinetics of desirudin? Is dose adjustment necessary in renally impaired patients?
7. What drug-drug interaction studies were conducted by the sponsor with desirudin?
8. What is the effect of hepatic impairment on the pharmacokinetics of ondansetron? Is dose adjustment necessary in patients with hepatic impairment?

Recommendation: This NDA is fileable from the Clinical Pharmacology and Biopharmaceutics perspective.

Comment to the sponsor: none

/S/

Sandip K. Roy, Ph.D.
Clinical Pharmacologist

8/28/2000
Date

FT initiated by Suresh Doddapaneni, Ph.D. /S/ 8/28/00

c.c. /NDA 21-271
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Appendix IV

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS Division of Pharmaceutical Evaluation II	
NDA:	**21-271**
Brand® Name	**[redacted]**
Generic	**Desirudin (rDNA)**
Submission Date:	**June 28, 2000**
Sponsor:	**Aventis**
Consult:	**Population PK, PK-PD**
Pharmacometrics Scientist:	**Sam H. Haidar, R.Ph., Ph.D.**

Background

NDA 21-271 for desirudin ([redacted]) injection was submitted by Aventis on June 28, 2000. The proposed indication for [redacted] is the prevention of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery. The recommended dose is 15 mg every 12 hours administered by subcutaneous injection, with the initial dose given up to 5 to 15 minutes prior to surgery.

Desirudin is a protein that is almost identical to hirudin, the naturally occurring anticoagulant found in the peripharyngeal glands of medicinal leeches. Desirudin is produced by recombinant DNA technology, which uses a strain of yeast with a chemically synthesized gene. Desirudin differs from natural hirudin by lacking a sulfate group on Tyr-63. In terms of activity, desirudin is a potent inhibitor of human thrombin.

This pharmacometric consult evaluated several studies that provided answers to important questions about desirudin properties. These are listed below.

Question: **What is the exposure/response relationship in healthy subjects/patients for desirudin?**

Study B104/1990 evaluated the pharmacokinetic-pharmacodynamic (PK-PD) relationship of desirudin and activated partial prothromboplastin time (APTT) in healthy volunteers.

Details of the study are given below.

Study B104/1990

Title: Pharmacokinetic-pharmacodynamic relationship for i.v. bolus injections of 0.1, 0.3, 0.5 or 1.0 mg/kg in 8 healthy volunteers each.

Methods:

In this study, single iv bolus injections of four dose levels: 0.1, 0.3, 0.5, or 1.0 mg/kg of desirudin (CGP 39 393) were administered to 16 healthy volunteers. Each volunteer received 2 of the 4 doses, so that each dose was tested in 8 volunteers total.

Sampling:

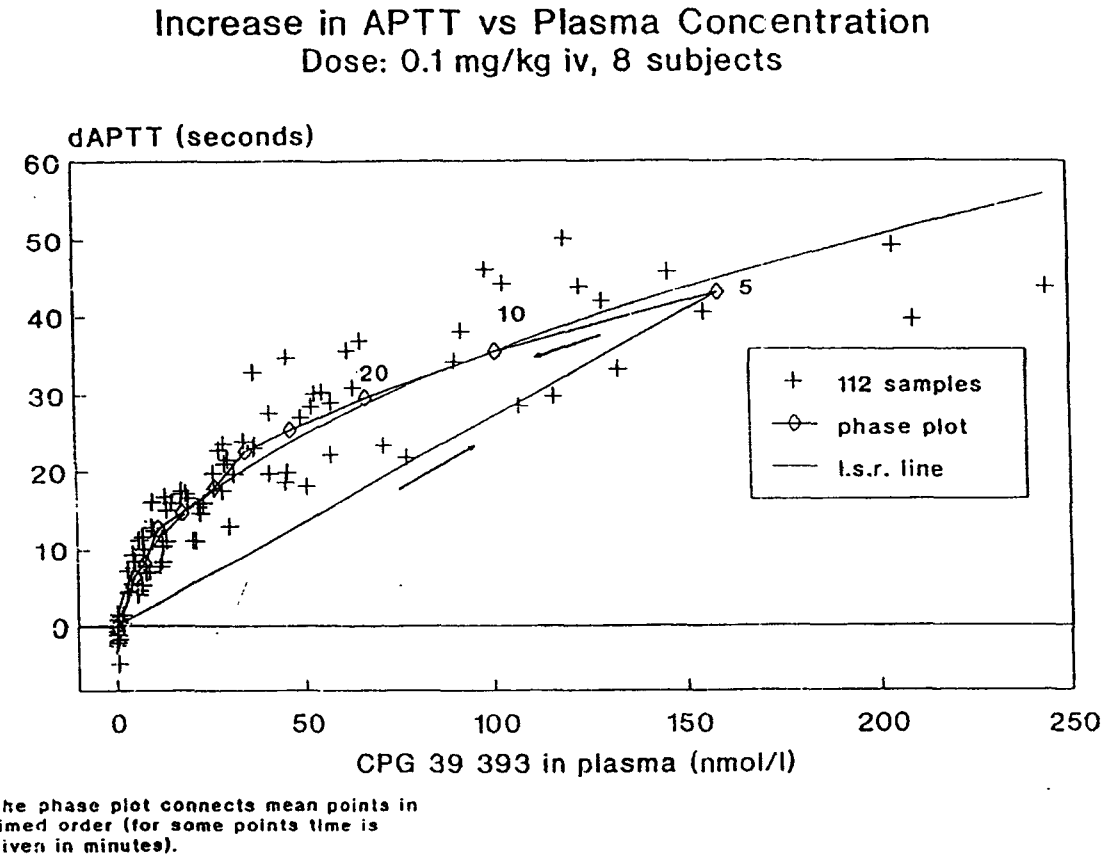

Figure 2. Time-ordered plot of desirudin plasma concentrations vs. changes from baseline for APTT (dAPTT) following the i.v. administration of 0.1 mg/kg (lowest dose).

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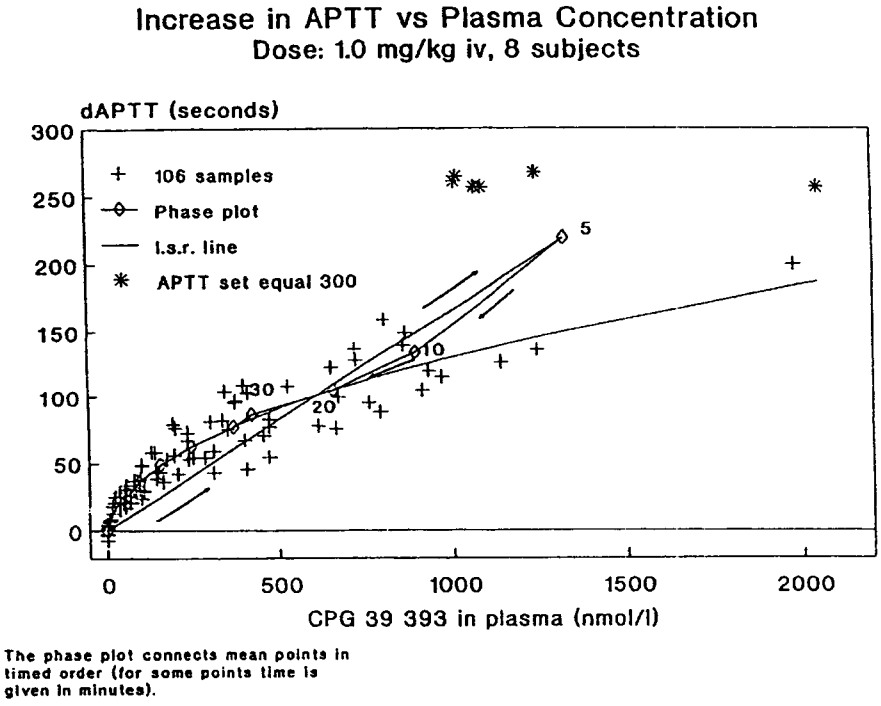

Figure 3. Time-ordered plot of desirudin plasma concentrations vs. changes from baseline for APTT (dAPTT) following the i.v. administration of 1 mg/kg (highest dose).

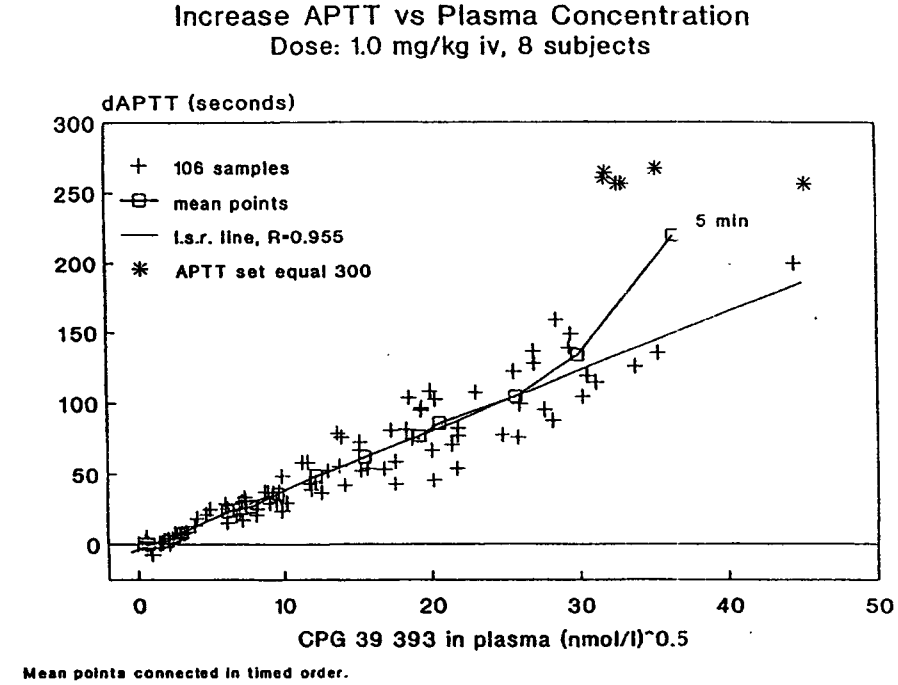

Figure 4. Changes from baseline for APTT (dAPTT) as a function of the square root of desirudin plasma concentrations following the i.v. administration of 1 mg/kg (highest dose). LSR is least squares regression.

Reviewer's Comments:

1. **The effect of desirudin on APTT appears almost immediately (no lag time) following i.v. administration. Effect is closely related to drug concentration, although there is a delay in termination of the effect after concentrations had fallen below detectable levels.**
2. **The sponsor constructed "hysteresis" plots for the various doses (e.g., Figure 2) to show equilibration delay between plasma concentrations and APTT changes. This is inappropriate here because hysteresis plots require the measuring of drug levels on the upswing (as drug concentration increases) as well as during the terminal phase. Thus, two effect measurements may be obtained for the same concentration. With i.v. bolus dosing, initial concentration is already near C_{max}, therefore, concentration data during the upswing would be lacking.**
3. **The sponsor developed a PK-PD model that relates changes in APTT as a function of the square root of plasma concentrations. Although the model produced reasonable fits, its use may be of limited value due to practical reasons (dealing with square root of concentration).**

Question: Is desirudin dose proportional?

Study C.R.B. R 9/1992 evaluated the dose proportionality of desirudin administered by i.v. infusion to patients with stable coronary artery disease.

Details of the Study and results are given below.

Study C.R.B. R 9/1992

Title: Pharmacokinetics of desirudin given as a 6-hour intravenous infusion of ascending doses in patients with stable coronary artery disease.

Methods:
This was a single-center, single-blind, placebo-controlled, ascending dose study in patients (N = 39) with stable coronary artery disease. The patients ranged in age between 42-71 years. Treatments were organized in five blocks of 8 patients each, 6 receiving active drug and 2 receiving placebo. Active treatment consisted of a 6-hour infusion of one of the following: 0.02, 0.05, 0.1, 0.2 or 0.3 mg/kg/hour of desirudin.

Sampling:
Plasma levels for the determination of desirudin levels were collected at 0, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0. 6.018, 6.17, 6.33, 6.5, 6.75, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 14, and 24 hours post start of infusion. Desirudin concentrations were measured using ELISA.

Pharmacokinetics:
The pharmacokinetics of desirudin were described using non-compartmental analysis.

Results:

Figure 4 illustrates dose-adjusted plasma concentration time profiles for desirudin following single dose administration of desirudin by i.v. infusion (0.02 and 0.3 mg/kg/hr for 6 hours).

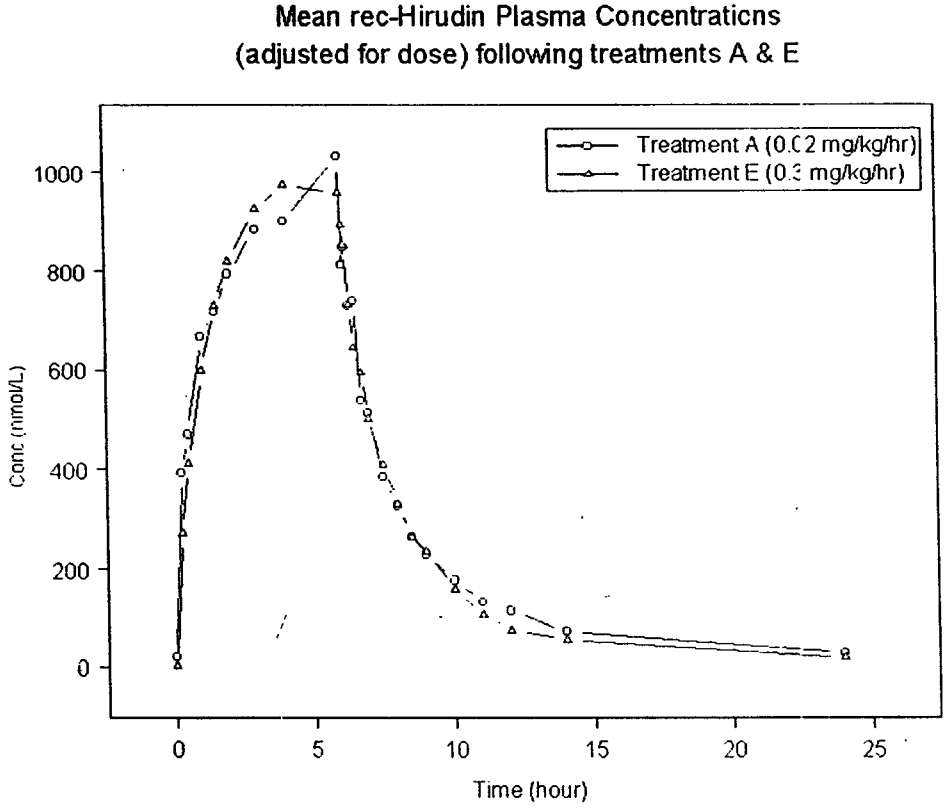

Figure 4. Desirudin plasma profiles, adjusted for dose, following single i.v. infusion doses (0.02 and 0.3 mg/kg/hr) in men with stable coronary artery disease.

Table I. Mean (S.D.) PK parameters for desirudin following single i.v. infusion doses in men with stable coronary artery disease.

Dose (mg/kg/h)	C_{max} (nmol/L)	T_{max} (h)	AUC (nmol/L/h)	$T_{1/2}$ (h)
0.02	25.8 (8.5)	6	176(6.8)	2.72
0.05	67.6(20)	5	388(139)	2.33
0.1	122(19)	6	792(145)	2.98
0.2	229(38)	6	1408(175)	3.11
0.3	317(65)	4	2133(483)	1.96
		Adjusted for Dose		
0.02	25.8		176	
0.05	27.0		155	
0.1	24.4		158	
0.2	22.9		141	
0.3	21.1		142	

Reviewer's Comments:

1. **Desirudin appears to be dose proportional over a dose range that extends beyond the proposed dosing.**

Question: What are the population PK and PD in patients? What patient covariates were found to be significant?

Study RH/E23 evaluated the population PK and PD in patients undergoing elective total hip replacement.

Details of the Study and results are given below.

Study RH/E23

Title: Population Pharmacokinetic and Pharmacodynamic evaluations in patients undergoing elective total hip replacement.

Methods:
Data used for the population PK analysis came from a Phase IIb dose finding trial which compared the efficacy of three dose levels of desirudin with that of unfractionated sodium heparin, administered prophylactically twice daily for 11 days to orthopedic patients undergoing total hip replacement therapy. There were a total of 301 patients available for the PK analysis (10 mg n = 101, 15 mg n = 97, and 20 mg n = 103). There were two plasma samples per patient for the determination of desirudin levels and aPTT. Additionally, one pre-treatment baseline measurement of aPTT was taken.

Previous i.v. and s.c. studies indicated that the concentration time profile of desirudin followed a 3-compartment model with first order absorption. In this study, however, the sponsor used a 1-compartment model. The sparse nature of the data (two per patient) did not allow for the precise estimation of the parameters of a more complex model. Additionally, lack of sampling in the absorption phase necessitated the use of a fixed value for ka (0.3012 hr^{-1}), which was estimated from previous studies.

The error model for the PK parameters assumed a log linear normal distribution as shown below:

$$cl_i = cl \bullet e^{\eta i_1}$$
$$v_i = v \bullet e^{\eta i_2}$$

where ηi_1 and ηi_2 are independantly normally distributed random effects with mean of 0 and variances Ω_1 and Ω_2, respectively.

Demographic factors evaluated included age, weight, creatinine clearance, and gender.

Results:

The final mixed effect model (accounting for body weight and creatinine clearance) is given below:

$$cli = (\theta_1 + \theta_2 \frac{renl_i - 80}{10}) \bullet e^{\eta_1 i}$$

$$vi = (\theta_3 \frac{wt_i}{10}) e^{\eta_2 i}$$

where *renl* and *wt* are the calculated renal creatinine clearance (mL/min) and body weight (kg) of the individual. Both are divided by 10 for display purposes. θ_1 is the expected desirudin clearance of an individual in the population with 80 (mL/min) creatinine clearance. θ_2 is the increase in clearance of desirudin per 10 mL/min increase in real function. θ_3 is the expected volume per 10 kg of body weight.

Table II below lists the PK parameter estimates and relevant variabilities.

Figures 5 through 8 are diagnostic plots showing the effect of two covariates (age and weight) on the variability of PK parameters (Cl and V): prior to (Figures 5 and 6) and following (Figures 7 and 8) incorporation of weight and creatinine clearance into the model.

Table II. Population PK parameter estimates (standard error)

PK Parameter	Parameter Estimate (standard error)	Intersubject Variability (%)
Cl (L/hr)	θ_1 (L/hr) = 10.9 (0.23)	27.1
	θ_2 (10^{-1}L/hr.min/mL) = 1.1 (0.02)	
V (L)	θ_3 (10^{-1}L/kg) = 3.23 (0.10)	34.1

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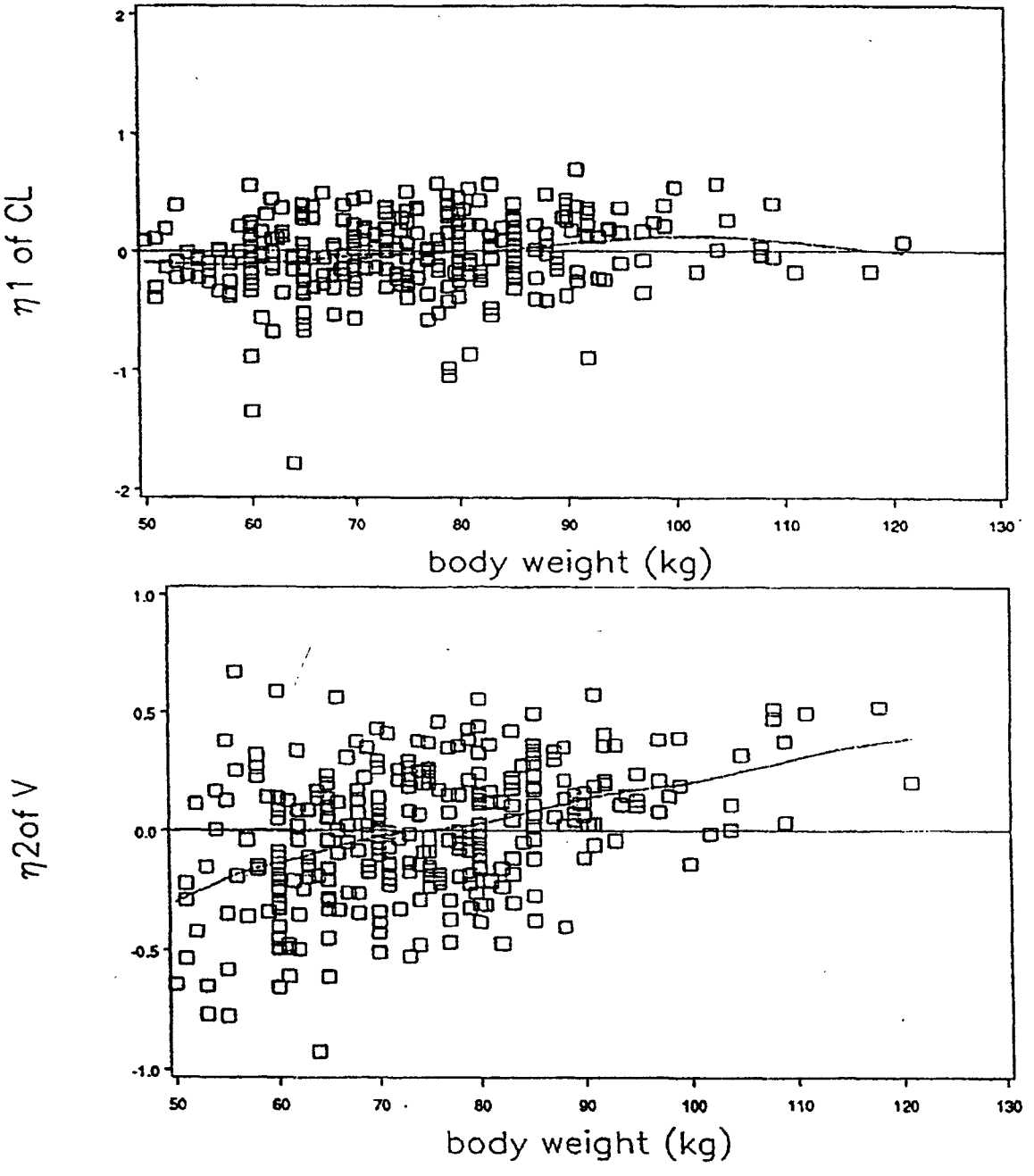

Figure 5. Intersubject variability in clearance (Cl) and volume of distribution (V) as a function of body weight prior to incorporation of creatinine clearance and body weight into the model (final step). Note the effect of body weight on volume of distribution.

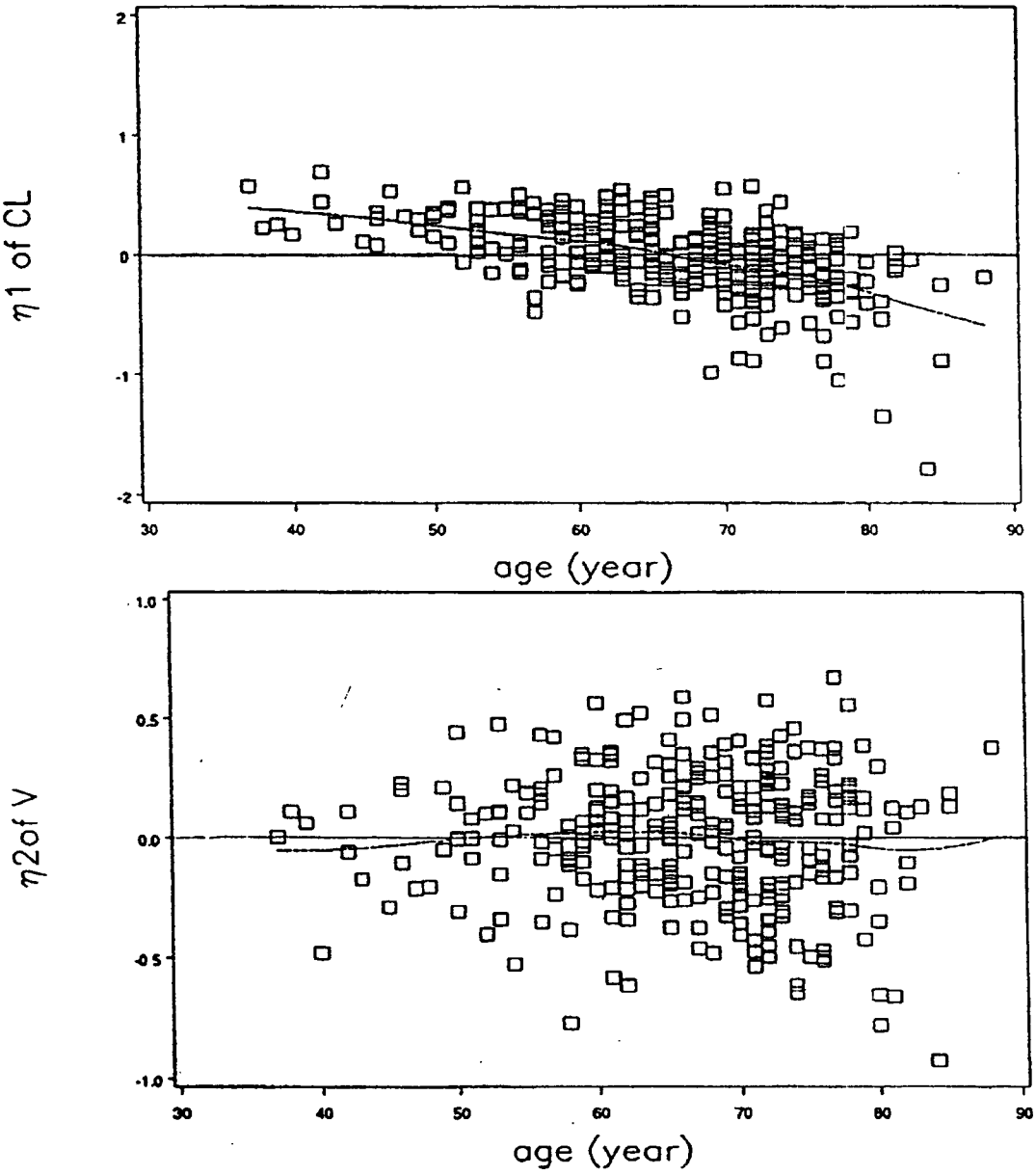

Figure 6. Intersubject variability in clearance (Cl) and volume of d.stribution (V) as a function of age prior to incorporation of creatinine clearance and body weight into the model (final step). Note the decreased Cl as age increases beyond 70.

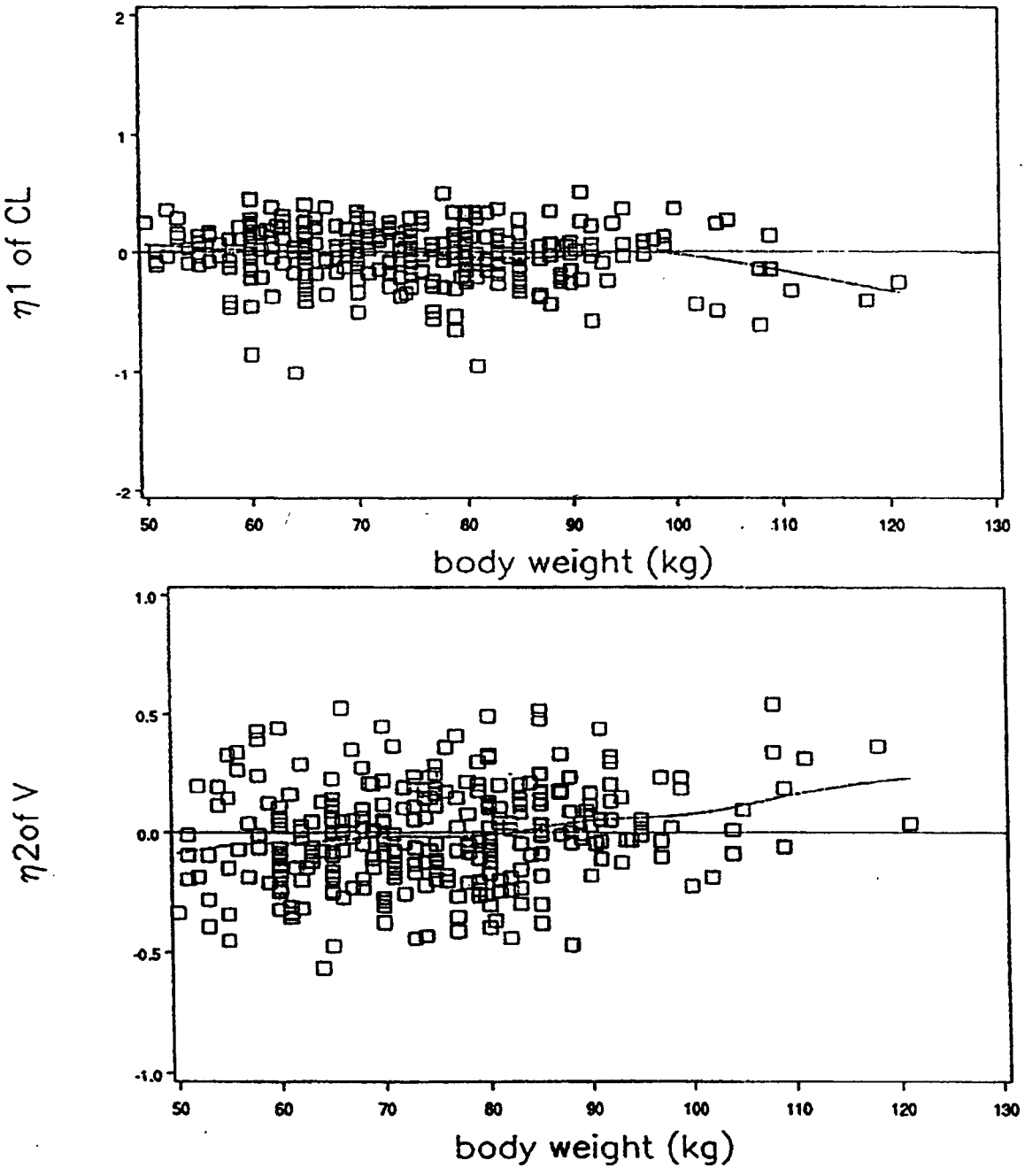

Figure 7. Intersubject variability in clearance (Cl) and volume of distribution (V) as a function of body weight after incorporation of creatinine clearance and body weight into the model (final step). Note that the effect of body weight on volume of distribution has almost disappeared.

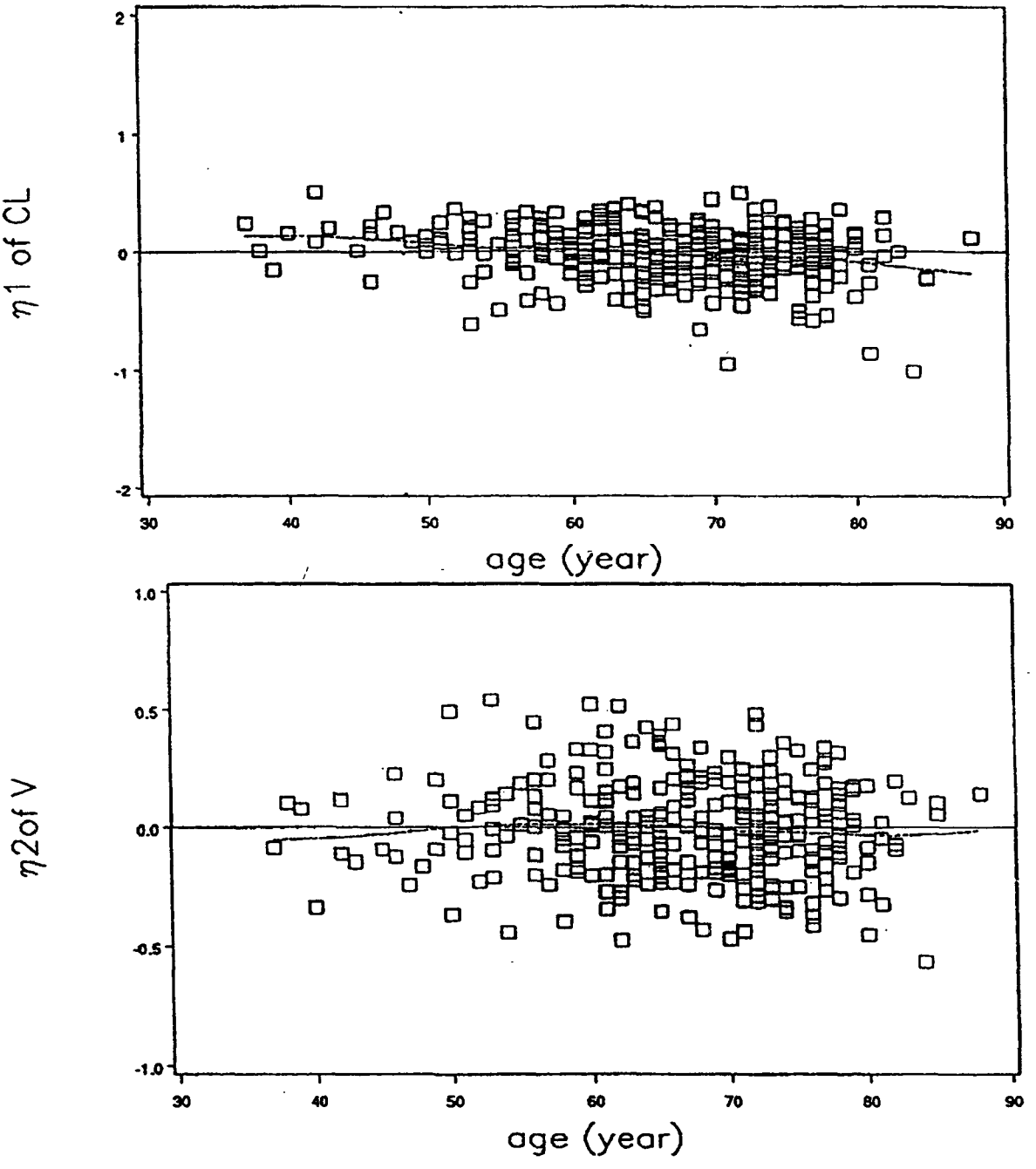

Figure 8. Intersubject variability in clearance (Cl) and volume of distribution (V) as a function of age after incorporation of creatinine clearance and body weight into the model (final step). The relationship between age and clearance seems to have been greatly reduced.

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