

Center for Drug Evaluation and Research

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Appendix A, page 71 through Appendix A4.6, page 91

A. Study reports**A1. In vitro metabolism studies****A1.1. Report DM2: In vitro metabolism of UK-92480 in hepatic microsomes from rat, dog, rabbit, and man.**

A1.1.1. Methods This study investigated the in vitro metabolism of sildenafil by hepatic microsomes of rat, dog, rabbit, and man. The cytochrome content was determined spectrophotometrically. Incubations were carried out in sildenafil 1 μM and cytochrome P450 0.4 mM in a total volume of 12 mL.

A1.1.2. Results The disappearance half-life values are shown in Table 41 below. The disappearance of sildenafil was accompanied by the formation of a metabolite identified as UK-103,320.

Table 41. Disappearance half-lives for sildenafil in hepatic microsomes (Report DM2).

	$t_{1/2}$ min		$t_{1/2}$ min
Rat		Dog	38
Male	2	Rabbit	113
Female	129	Human	45

A1.2. Report DM3: In vitro metabolism of UK-92480 in human liver microsomes enzymology of UK-103,320 formation.

A1.2.1. Source documents NDA 20-895, vol 1.34; electronic document 46815069.pdf.

A1.2.2. Objectives The aim of this study was to identify the enzymes responsible for the N-demethylation to UK 103,320.

A1.2.3. Methods Hepatic microsomes were prepared from individual human livers or a combination of 4 human livers by the process of differential centrifugation. For each of the assays used, the final incubation volume was 1 mL. A sildenafil substrate concentration of 0 to 750 μM was chosen to look at the kinetics of UK-103,320 formation, and the effects of specific inhibitors of various P450 isoforms on the metabolism of sildenafil were investigated. Table 1 shows the concentrations of inhibitors used, the isoform which they specifically inhibit and the percentage of inhibition of probe substrate for that isoform. These inhibitors were co-incubated with sildenafil at 2.5 and 250 μM .

Table 42. P450 inhibitors (Report DM3).

P450	Inhibitor	μM	Inhibition (%)	P450	Inhibitor	μM	Inhibition (%)
CYP1A2	Furafylline	1	59	CYP2D6	Quinidine	2.5	82
		10	95			25	95
CYP2C9	Sulphaphenazole	2.5	53	CYP3A4	Ketoconazole	2.5	79
		25	85			25	88

In addition, a bank of 14 human livers was used to assess sildenafil metabolism. Microsomes from these livers had been previously characterized for P450 isoform activity. A correlation was performed between sildenafil metabolism at 2.5 and 250 μM and each isoform activity across the human liver bank. The correlation was weighted by using the logarithm of the sildenafil rates and P450 probe substrate activities to minimize the influence of high-activity livers.

The formation of the metabolite UK-103,320 from sildenafil (2.5 and 250 µM) was assessed in microsomes from AHH-1 TK+/- cells engineered to express one of CYP1A2, CYP2C9, CYP2D6, CYP2E1, or CYP3A4 as the cell's only P450. The kinetics of UK-103,320 formation were investigated in cells expressing CYP3A4 and CYP2C9.

A1.2.4. Results

The rate of formation of UK-103,320 in human liver microsomes was linear with time up to 60 minutes and protein up to 0.1 mg/mL microsomal protein. The mean kinetic parameters for 3 livers are given in Table 43 below. Figure 8 below shows the effect of specific CYP inhibitors on the metabolism of sildenafil. The results of the inhibition study show that CYP3A4 and CYP2C9 are involved in the formation of UK-103,320. Table 44 below shows the results of analyses of the correlation across a bank of 14 human livers which indicate a strong correlation between the formation of UK-103,320 and the activity of CYP3A4 and CYP2C9. This is further illustrated in Figure 9 below. Figure 10 below shows the results of the study done with cells lines expressing CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. At a concentration of 2.5 µM of sildenafil both CYP2C9 and CYP3A4 mediated UK-103,320 formation with CYP3A4 producing a rate 20 times that of CYP2C9. At 250 µM CYP2D6, CYP2C9 and CYP3A4 mediated UK-103,320 formation. However, the rate produced by CYP2D6 was considered negligible at the concentration level studied. This rate increased 20 fold for CYP3A4 and 13 fold for CYP2C9 when going from a 2.5 µM to 250 µM.

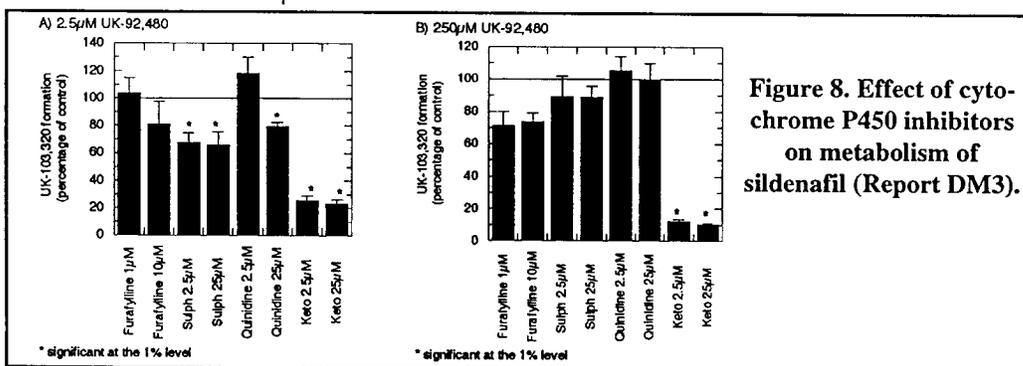


Figure 8. Effect of cytochrome P450 inhibitors on metabolism of sildenafil (Report DM3).

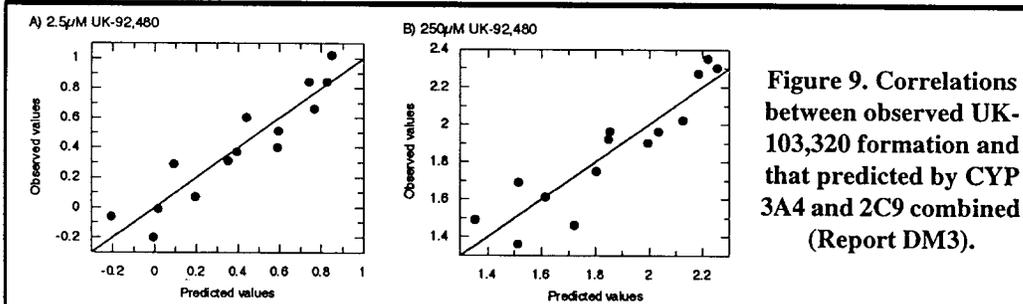


Figure 9. Correlations between observed UK-103,320 formation and that predicted by CYP 3A4 and 2C9 combined (Report DM3).

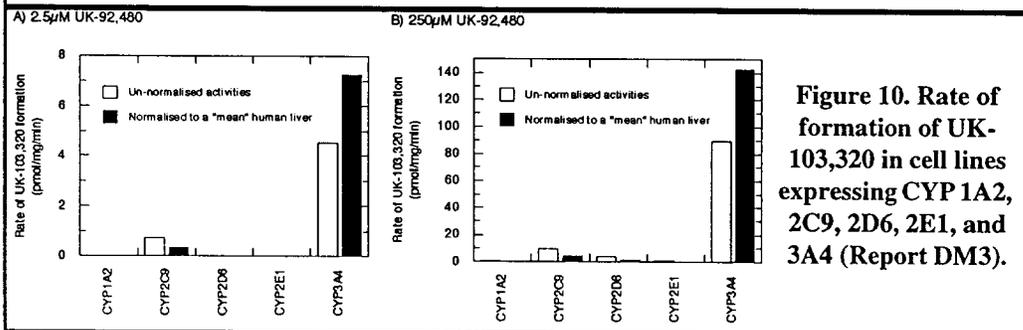


Figure 10. Rate of formation of UK-103,320 in cell lines expressing CYP 1A2, 2C9, 2D6, 2E1, and 3A4 (Report DM3).

Table 43. UK-103,320 formation in human liver microsomes (Report DM3).

	Affinity	
	High	Low
K_m (μM)	6.0±2.5	81±45
V_{max} (pmol/mg/min)	22±9.7	138±77

Table 44. Correlation between rate of UK-103,320 formation and P450 isoform activity (Report DM3).

Isoform	Substrate	Sildenafil μM^a		Isoform	Substrate	Sildenafil μM	
		2.5	250			2.5	250
CYP1A2	Caffeine	0.49	0.53	CYP2D6	Bufuralol	0.34	0.33
CYP2A6	Coumarin	0.24	0.44	CYP2E1	Chlorzoxazone	0.36	0.49
CYP2C9	Phenytoin	0.77*	0.80*	CYP3A4	Testosterone	0.87*	0.84
CYP2C19	S-mephenytoin	0.48	0.31				

a. *P<0.01 by sponsor's analysis.

A1.2.5. Conclusion

Sildenafil is metabolized to UK-103,320 in human liver microsomes by two enzymes. CYP2C9 was the high affinity enzyme with a K_i of 6 μM . CYP3A4 was considered to be the low affinity enzyme with a K_i of 81 μM .

A1.3. Report DM4: In vitro inhibition studies on UK-92480 in human liver microsomes.

A1.3.1. Source documents

NDA 20-895, vol 1.34.

A1.3.2. Objectives

The objective of the study was to investigate the potential of sildenafil to inhibit 6 cytochrome P450 isoforms considered to be of general importance in drug metabolism. These isoforms are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4. The study was conducted in vitro with human liver microsomes using probe substrates for these isoforms.

A1.3.3. Results

The estimated IC_{50} for the various isoforms tested are summarized in Table 45 below.

Table 45. Inhibition of CYP isoforms by sildenafil (Report DM4).

Isoform	Substrate	IC_{50} μM	Isoform	Substrate	IC_{50} μM
CYP1A2	Phenacetin	~300	CYP2D6	Bufuralol	>300
CYP2C9	Phenytoin	150	CYP2E1	Chlorzoxazone	>1000
CYP2C19	S-mephenytoin	~300	CYP3A4	Felodipine	>300

A1.3.4. Conclusion

Since the expected peak plasma concentrations in the clinically relevant dosing range (25 to 100 mg) is around 1 μM , it is unlikely that sildenafil will inhibit any of the relevant CYP isoforms to any significant extent, and thus no drug-drug interactions are expected based on inhibition of the P450 system.

A1.4. Report DM5: In vitro metabolism and P450 inhibition studies of UK-103,320 in human liver microsomes.

A1.4.1. Source documents

NDA 20-895, vol 1.34; electronic document 46815067.pdf.

A1.4.2. Objectives

The objectives of this study were to investigate whether UK-103,320 is metabolized by cytochrome P450 and also to determine the its potential to inhibit 6 cytochrome

P450 isoforms considered of general importance in drug metabolism (viz CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4).

A1.4.3. Methods

The studies were conducted in vitro in human liver microsomes.

A1.4.4. Results

The results suggest that UK-103,320 is metabolized by the CYP450 system. Two putative metabolites were identified—UK-321,120 (N-desmethyl) and UK-331,849 (removal of two-carbon fragment from piperazine ring). Scheme 1 shows the partial metabolic scheme for UK 103,320 in human liver microsomes.

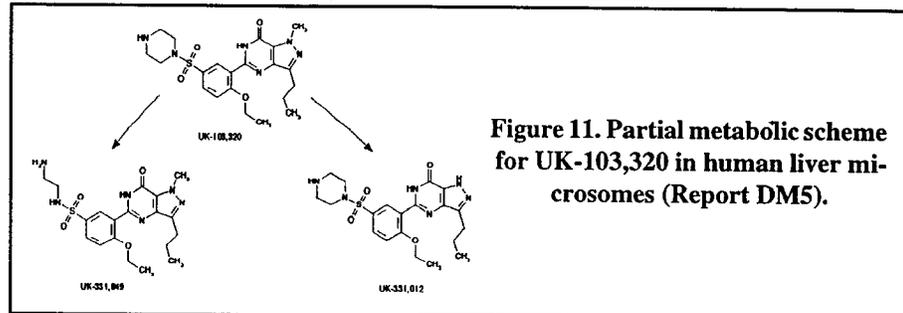


Figure 11. Partial metabolic scheme for UK-103,320 in human liver microsomes (Report DM5).

Moreover, the results of this study indicate that UK-103,320 is a very weak inhibitor of the CYP isoforms investigated, as shown in Table 46 below. The IC₅₀'s are well above the expected peak plasma concentrations for this metabolite.

Table 46. Inhibition of CYP isoforms by UK-103-320 (Report DM5).

Isoform	Substrate	IC ₅₀ μM	Isoform	Substrate	IC ₅₀ μM
CYP1A2	Phenacetin	>1000	CYP2D6	Bufuralol	71
CYP2C9	Diclophenac	>1000	CYP2E1	Chlorzoxazone	>1000
CYP2C19	S-mephenytoin	>300	CYP3A4	Felodipine	>300

A1.5. Report DM34: In vitro interaction between UK-92480 and the CYP3A4 substrates terfenadine and testosterone in human liver microsomes.

A1.5.1. Source documents NDA 20-895, vol 1.34.

A1.5.2. Objectives The objective of this study was to investigate the potential of sildenafil to inhibit the metabolism of terfenadine and testosterone in human liver microsomes.

A1.5.3. Results Figure 12 below shows the effect of sildenafil on the activity of testosterone 6-β-hydroxylase and terfenadine hydroxylase.

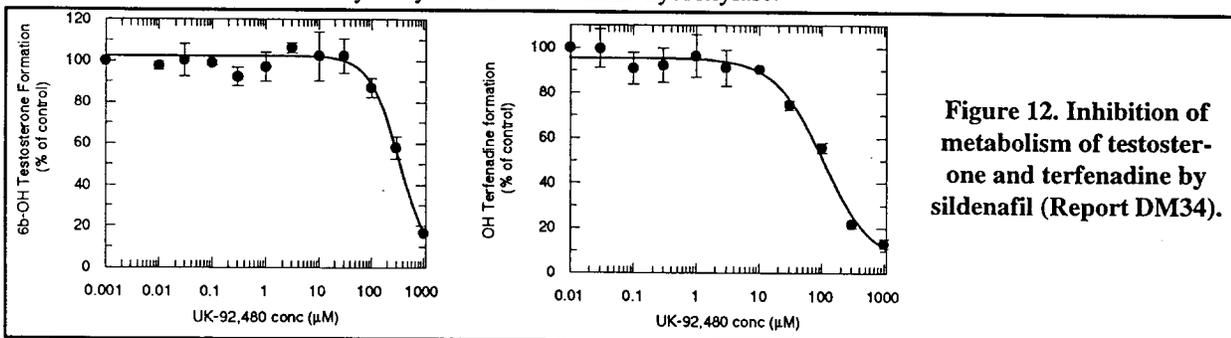


Figure 12. Inhibition of metabolism of testosterone and terfenadine by sildenafil (Report DM34).

The IC₅₀ of sildenafil was greater than 300 μM for testosterone and around 100 μM for terfenadine. The K_i was estimated to be 50 μM. Since the peak plasma sildenafil concentrations are expected to be around 3 μM, these results suggest there will be no clinically significant interactions between sildenafil and CYP3A4 substrates.

A2. Population pharmacokinetic and pharmacodynamic analysis of sildenafil phase III data.

A2.1. Methods

A2.1.1. Data collection

A population pharmacokinetic strategy was incorporated into 5 phase III clinical study protocols (studies 148-102, 148-103, 148-104, 148-106 and 148-364). Two thousand seventy-seven subjects (1335 on sildenafil) were asked to take an additional dose of study drug prior to their scheduled clinic visits on 4 or 5 occasions throughout the study. A single plasma sample was obtained at random times after dosing and assayed for both drug and metabolite UK-103,320 concentrations. A total of 4582 samples were assayed (3.4 samples per individual). Data from individual studies were combined into one dataset.

A2.1.2. Pharmacokinetic modeling

Formal population pharmacokinetic analysis was performed using the nonlinear mixed effects modeling approach. The software package NONMEM version IV, level 2.2 was used to derive the population mean (and variance) values for specific pharmacokinetic parameters, such as apparent clearance and apparent volume of distribution, and these were subsequently used to derive estimates of exposure (AUC). Appropriate structural pharmacokinetic models were fitted to both the parent drug and metabolite using standard population pharmacokinetic methodology.

Both linear and nonlinear relationships between the individual parameter estimates and the various covariate indices for demography, biochemistry and concomitant medication were explored and, where indicated, used to refine the population model and characterize sources of inter-individual and intra-individual variability. Covariates were added to the model if they significantly decreased the objective function by 0.1% level of significance. Covariates were removed from the model if ± 2 SE of the resultant parameter estimate encompassed 0. The significance of each of the covariates in the fully developed model was further tested by fixing each structural model parameter used to characterize the covariate relationship to a null value and performing reduced-versus-full model pair comparisons. The resultant final model only contained covariates that met the pre-defined statistical criteria. The clinical relevance of any relationship was also considered.

For the drug pharmacokinetic model, model building was initiated on a test database which comprised studies 148-102, 148-103 and 148-104. A validation dataset comprised of studies 148-106 and 148-364 was used to test the predictive performance of the derived population model from the test data. These datasets were subsequently combined and the resultant population model refined and finalized. As part of the model-building process, the validity of the population model was assessed via deletion diagnostics; i.e., the population model parameter values were re-estimated following sequential removal and replacement of individual study data.

A2.1.3. Pharmacokinetic-pharmacodynamic modeling

The relationship between the AUC of the parent drug and metabolite to questions 3 (*How often were you able to penetrate your partner?*) and 4 (*How often were you able to maintain your erection after you had penetrated your partner?*) of the International Index of Erectile Function (IIEF) sexual function questionnaire were investigated. The responses to these effectiveness questions were recorded as follows: (0) did not attempt an intercourse, (1) almost never or never, (2) a few times, (3) sometime, (4) most times, or (5) almost always or always.

Asymptotic E_{\max} models with baseline and placebo components were used in these analyses. A number of independent variables were incorporated in these models including dose, drug AUC, metabolite AUC and both drug and metabolite AUC concurrently.

Relationships between sildenafil dose and the individual estimates of both AUC and C_{\max} to the various adverse events were explored graphically.

A2.2. Results

Figure 13 below shows the drug concentrations for parent drug and metabolite. Insets show log-plots of the same data, omitting concentration values below 1 ng/mL.

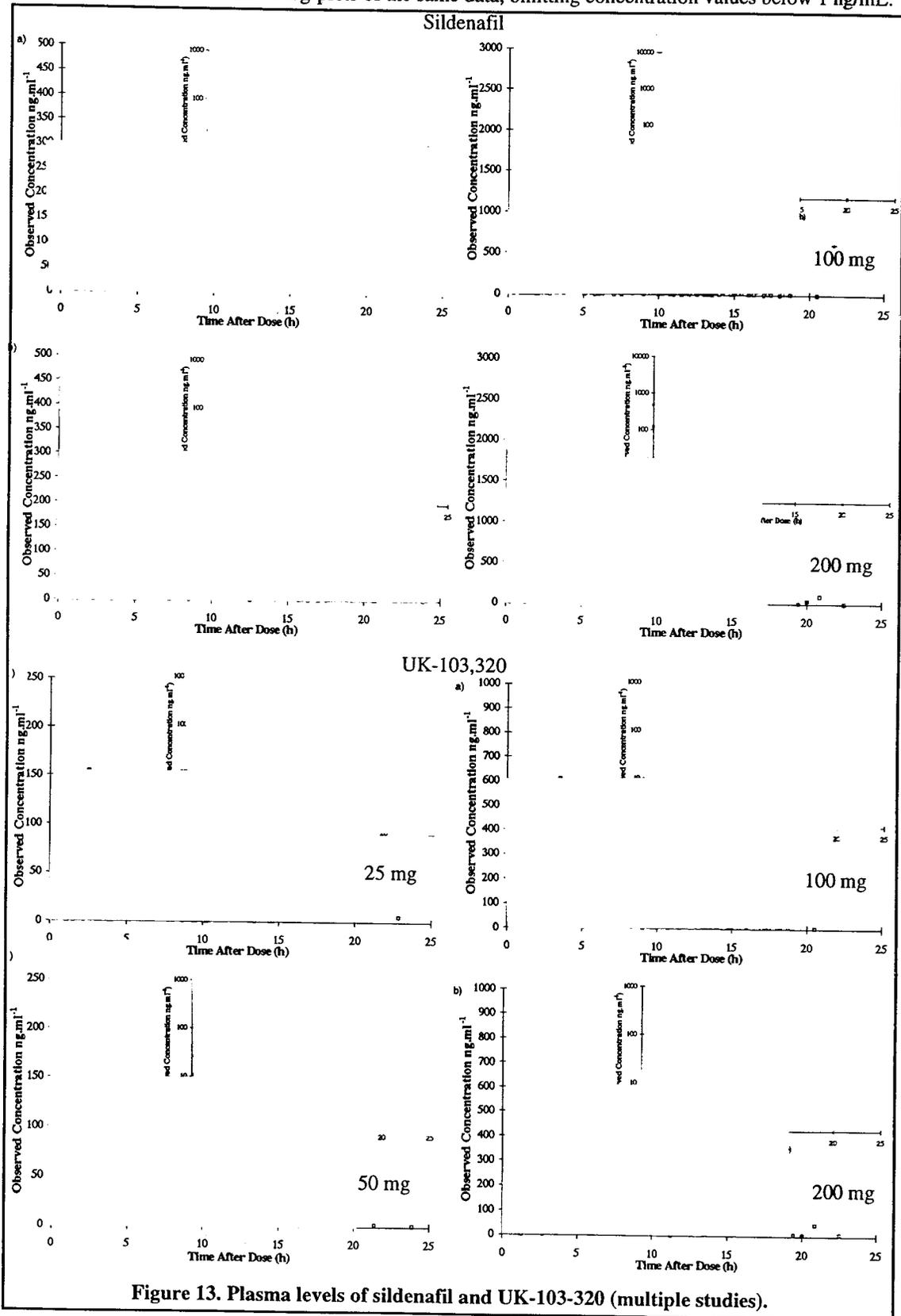


Figure 13. Plasma levels of sildenafil and UK-103-320 (multiple studies).

A2.2.1. Sildenafil pharmacokinetics

According to the sponsor, the sildenafil plasma concentration-versus-time data were appropriately described by a 1-compartment disposition model with first-order input. There was no evidence in the goodness-of-fit plot (Figure 14 below) that a more complicated structural model would be required.

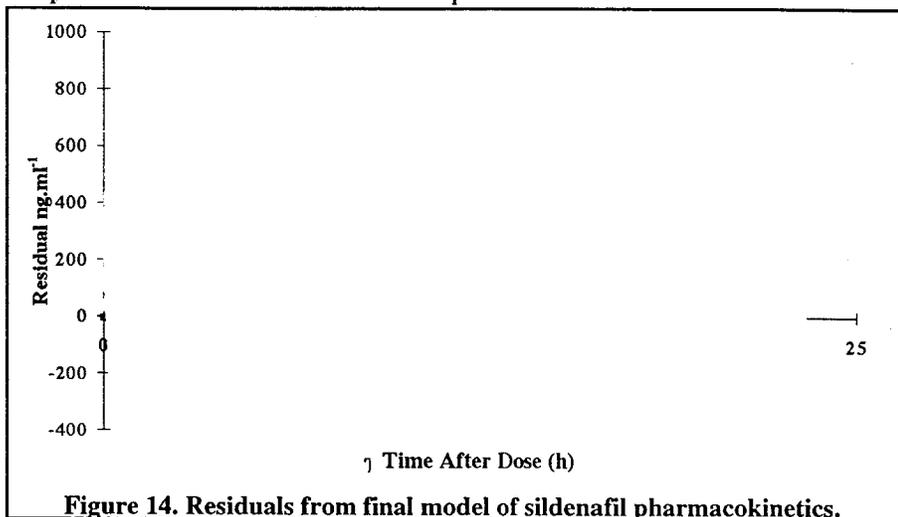


Figure 14. Residuals from final model of sildenafil pharmacokinetics.

Three covariates considered to statistically and clinically influence the apparent clearance of sildenafil were age, AST concentration, and whether patients were receiving CYP3A4 inhibitors. There was a 4% decrease in Cl/F for every decade increase, a 6% decrease in Cl/F for every 10-unit increase in AST, and a 14% decrease with co-administration of CYP3A4 inhibitors. For apparent volume of distribution, weight was considered to be a significant covariate. There was a 6% increase in V/F for every 10-kg increase. Figure 15 below shows the relationships between some of these continuous covariates and the structural model parameters they influence.

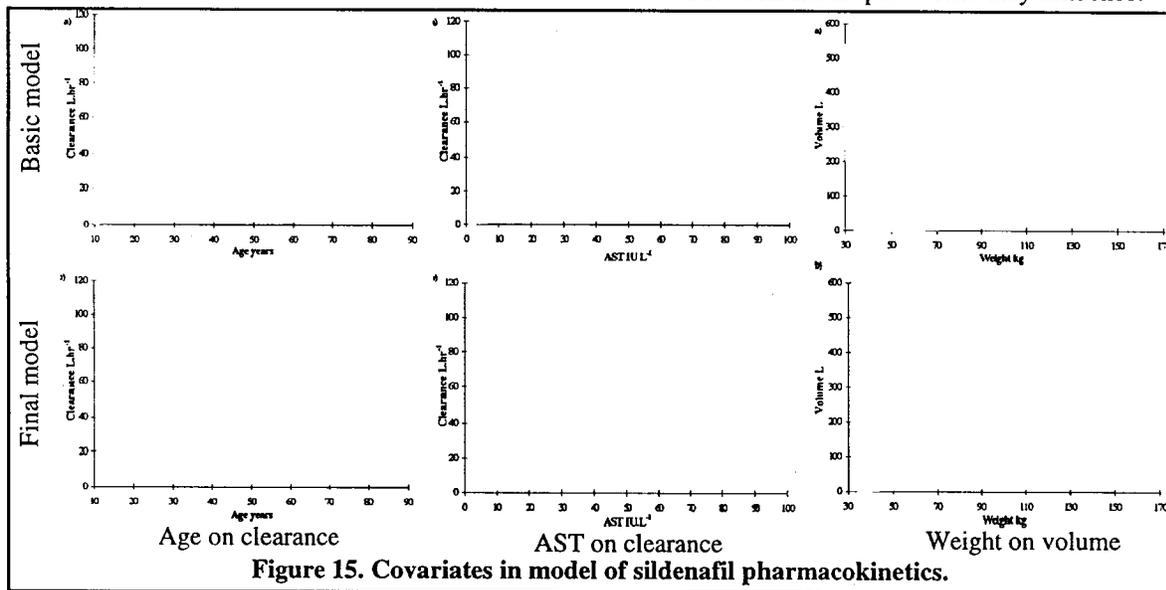


Figure 15. Covariates in model of sildenafil pharmacokinetics.

The model included 2 absorption rates, representing the fasted and fed states.

Non-proportionality of plasma levels of sildenafil with dose was best described by a 40% increase in bioavailability associated with the 200-mg dose.

Figure 16 below gives the goodness of fit plots for the population predicted concentrations and the individual predicted concentrations versus observed final data

set concentrations. Table 47 below shows the estimated pharmacokinetic parameters following administration of sildenafil 25 to 200 mg. Table 48 below shows the effects of addition of covariates to the basic pharmacokinetic model for sildenafil, using the test dataset. Table 49 below shows the effect of additions and deletions in the covariates to the full pharmacokinetic model for sildenafil, using the final dataset. Table 50 below gives the structural and covariate parameter estimates for the population pharmacokinetic model for sildenafil after removal of component studies.

Table 47. Pharmacokinetic parameters (mean±SD) for final sildenafil model.

	25 mg	50 mg	100 mg	200 mg		25 mg	50 mg	100 mg	200 mg
AUC (ng.h/mL)	464±175	950±345	1963±859	5485±1964	CL/F (L/h)	60±18	58±17	58±18	41±12
C _{max} (ng/mL)	84±81	156±49	327±236	902±287	V/F (L)	302±76	299±75	309±88	210±55
T _{max} (h)	1.1±0.9	1.0±0.8	1.2±1.0	1.0±0.8	K _a (h ⁻¹)	13±26	15±28	14±25	21±37
T _{1/2} (h)	3.6±0.7	3.7±0.7	3.8±0.8	3.7±0.7	K _e (h ⁻¹)	0.20±0.04	0.20±0.04	0.19±0.04	0.19±0.03

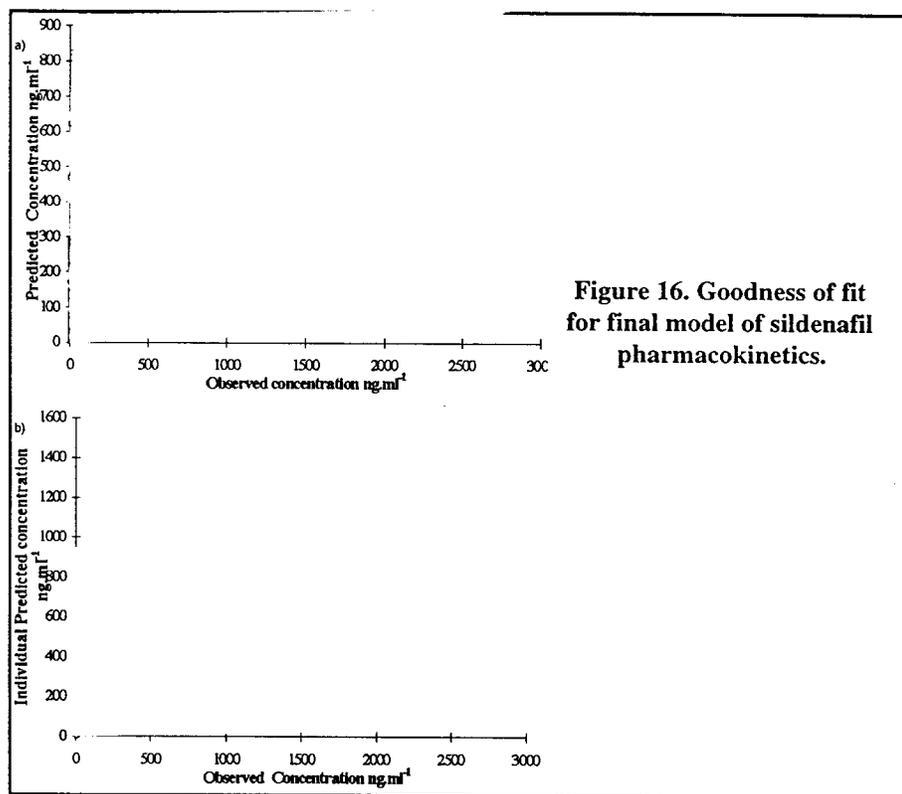


Figure 16. Goodness of fit for final model of sildenafil pharmacokinetics.

Table 48. Effect of addition of covariates to basic sildenafil model (test data).

Covariate model for CL/F				Covariate model for V/F			
Covariate	ΔFit	Covariate	ΔFit	Covariate	ΔFit	Covariate	ΔFit
Age	-48	Nitrate	-15	BSA	-56	MI	-16
CLcr	-29	AST	-15	Weight	-48	Subj	-16
ACEI	-28	Race	-11	Height	-29	Age	-14
Dose	-27			CCK	-22	CLcr	-13
				Dose	-21	AlkP	-12
				Bili	-20		

Table 49. Effect of changes in covariates on pharmacokinetic model for sildenafil (final dataset).

Covariate change	ΔFit	Decision	Covariate change	ΔFit	Decision	Covariate change	ΔFit	Decision
-Age on CL/F	+18	Keep	-Nitrate on CL/F	+3	Drop	-CCK, +Log(CCK)	+1	Drop
-CCK on CL/F	+1	Drop	-Race on CL/F	+23	Keep	-AST, +Log(AST)	-10	Log(AST)?
-AST on CL/F	+30	Keep	-Weight on V/F	+45	Keep	-AST, +ALT	-20	ALT?
-CCB ^a on CL/F	0	Drop	-MI on V/F	+20	Keep	-AST, +Log(ALT)	+10	Keep AST
-ACEI on CL/F	+7	Drop	-25/50mg on Bioavail	+5	Drop	-AST, +AlkP	+26	Keep AST
-3A4 inhib on CL/F	+15	Keep	-200mg on Bioavail	+32	Keep	-AST, +Log(AlkP)	+20	Keep AST
-Diuretics on CL/F	+2	Drop	-2 parameters ^b on K _a	+37	Keep	+CLcr	+7	Drop
-β-block on CL/F	+13	Keep						

a. Calcium channel blockers

b. No idea

Table 50. Effect of deletion of studies from final pharmacokinetic model for sildenafil.

	Study deleted							Study deleted					
	None	-364	-106	-104	-103	-102		None	-364	-106	-104	-103	-102
CL/F	1	1.02	1.04	0.98	0.98	0.98	3A4 inhib	1	1.01	1.01	0.97	1.02	1.01
V/F	1	1.00	1.03	0.95	0.99	1.04	β-block	1	1.16	0.92	0.99	1.01	0.96
K _a	1	0.94	0.98	1.00	1.04	1.07	Race	1	1.00	1.06	0.98	1.02	0.96
Resid	1	1.01	1.02	0.99	0.98	0.99	Weight	1	1.19	1.21	0.70	0.97	1.13
Age	1	1.52	1.38	0.96	0.95	0.27	MI	1	0.99	0.97	1.05	0.99	3.98
AST	1	0.59	1.29	1.16	0.85	0.95	200 mg	1	1.00	0	0.95	0.99	1.06

The population typical values were 59±1.4 L/h for clearance, 310±7 L for apparent volume of distribution, and 2.6±0.2 h⁻¹ for K_a. The inter-individual variability (mean±SE) was 29±20% for clearance, 20±50% for apparent volume of distribution, and 210±25% for K_a. The level of residual variability (CV±SE) was 48±12%.

A2.2.2. UK-103,320 pharmacokinetics

Figure 17 below shows the goodness-of-fit plot for the final population model for UK-103,320 for the population-predicted concentrations and individual predicted concentrations versus observed concentrations in the final dataset. Figure 18 below shows selected covariate relationships for the final population pharmacokinetic model. Table 51 below shows the effects of addition of covariates to the basic pharmacokinetic model for UK-103,320, using the test dataset. Table 52 below shows the effect of deletions of covariates to the full pharmacokinetic model for UK-103,320, using the final dataset. Table 53 below gives the structural and covariate estimates for the population pharmacokinetic model after removal of component studies.

Table 51. Effect of addition of covariates to basic UK-103,320 model (test data).

Covariate model for CL/F				Covariate model for V/F			
Covariate	ΔFit	Covariate	ΔFit	Covariate	ΔFit	Covariate	ΔFit
Dose	-105	3A4 inhib	-23	AST	-54	3A4 inhib	-19
CCB	-57	CCK	-20	CCB	-40	Diuretics	-17
CLcr	-52	ACEI	-15	Bili	-40	CS β-blocker ^a	-15
AST	-34	ALT	-13	CLcr	-29	Subject	-11
β-blocker	-29	BSA	-11	ALT	-25		
Subject	-29	AlkP	-11				

a. Cardio-selective β-blocker.

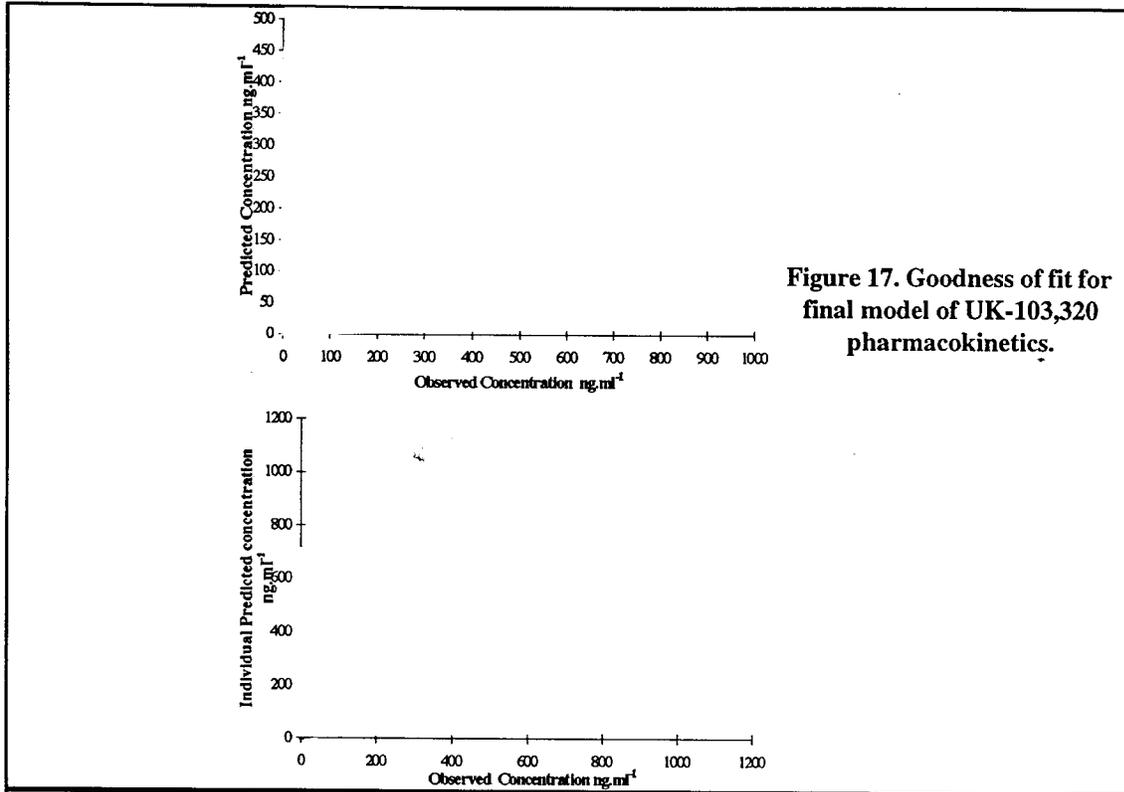


Figure 17. Goodness of fit for final model of UK-103,320 pharmacokinetics.

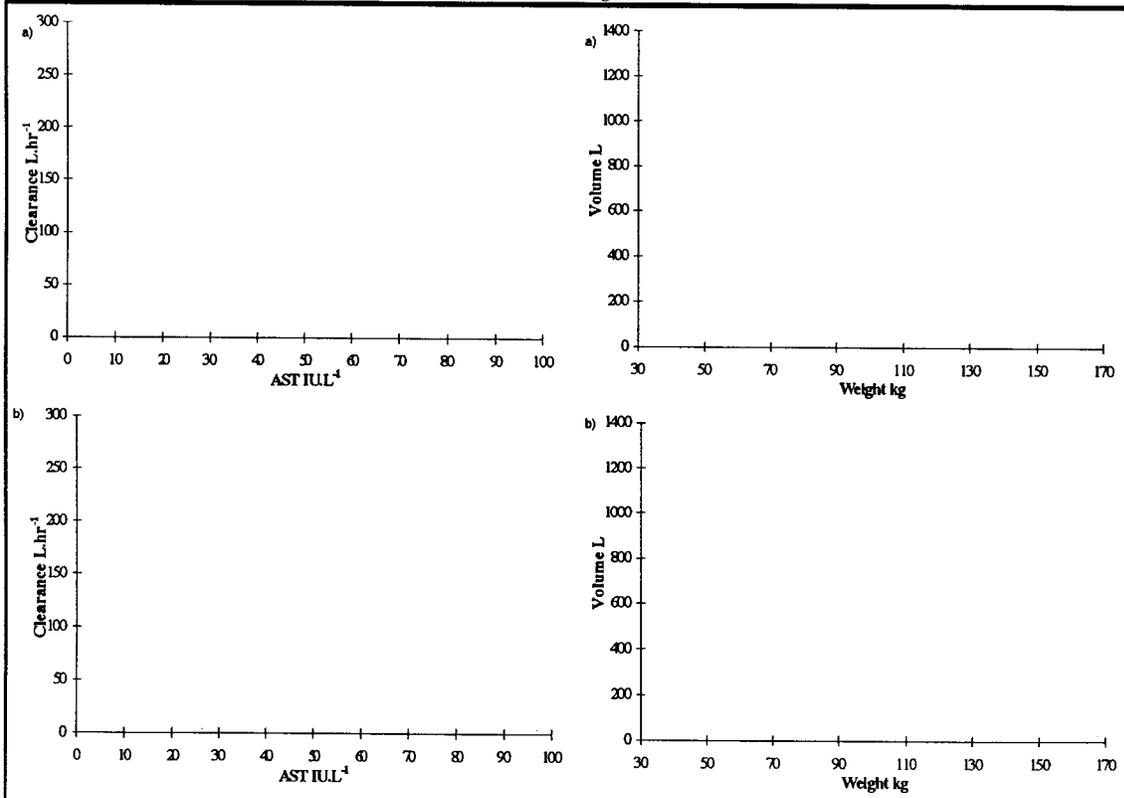


Figure 18. Selected covariate relationships in the final model of UK-103,320 pharmacokinetics.

Table 52. Effect of changes in covariates on pharmacokinetic model for UK-103,320 (final dataset).

Covariate change	ΔFit	Decision	Covariate change	ΔFit	Decision	Covariate change	ΔFit	Decision
-25/50mg	+48	Keep	-AST	+9	AST?	-2C4 inhib	+2	Drop
-200mg	+17	Keep	-ALT	+2	Drop	-Age	0	Drop
-CLcr	+3	Drop	-AlkP	+3	Drop	-Weight	+15	Keep
-CCK	+8	CCK?	-CCB	+21	Keep	-Diuretics	+12	Keep
-Bili	0	Drop	-ACEI	+3	Drop	-β-blockers	+96	Keep

Table 53. Effect of deletion of studies from final pharmacokinetic model for UK-103,320.

	Study deleted							Study deleted					
	None	-364	-106	-104	-103	-102		None	-364	-106	-104	-103	-102
CL/F	1	1.01	1.03	0.99	0.99	0.99	AST	1	0.56	1.00	0.75	1.00	1.04
V/F	1	1.02	0.97	0.98	0.97	1.05	CCB	1	0.96	0.90	1.03	1.12	0.97
K _a	1	0.97	0.96	1.04	1.04	0.99	Race	1	1.12	1.13	0.94	0.98	0.90
Resid	1	1.00	1.04	0.98	0.98	1.02	Weight	1	0.50	1.01	1.16	1.27	1.20
25/50 mg	1	0.76	1.29	1.03	0.91	1.10	Diuretic	1	0.96	1.17	0.88	1.07	0.93
200 mg	1	1.07	1.36	0.96	1.12	1.02	β-blocker	1	0.86	1.41	0.94	1.25	0.79

Three covariates were found to have a significant effect on the apparent clearance of UK-103,320. There was a 9% decrease in clearance for each 10-unit increase in AST. Loop diuretics and nonspecific β-blockers decreased CL/F by 31% and 54%, respectively. The relationship between weight and apparent volume of distribution predicted a 3% change in V/F for every 10-kg change in weight. The non-proportionality in bioavailability predicted a 13% decrease with the 25- and 50-mg doses and a 14% increase with the 200-mg dose, relative to the 100-mg dose. The population-typical values were 109±3.7 L/h for CL/F, 736±35 L for V/F, and 2.6±0.2 h⁻¹ for input rate. The inter-individual variability (mean±SE) were 49±21% for apparent clearance, 38±29% for V/F, and 292±21% for input rate. The level of residual variability was 48±12%.

A2.2.3. Pharmacodynamics

Asymptotic E_{max} models with placebo and baseline components were used in the efficacy analyses. A number of independent variables were incorporated into these models including dose, drug AUC, metabolite AUC, and both drug and metabolite AUC concurrently. The predicted parameters were the baseline value, a component for placebo response, the maximum response (E_{max}) and the value of the dependent variable that was associated with 50% of the E_{max} (D₅₀).

Effectiveness question 3¹: Table 54 below shows that irrespective of the estimation method adopted with NONMEM and the independent variable used, an additive model performed better than a proportional model (an absolute change in response from baseline was more appropriate than a relative change). The table also shows that neither drug nor metabolite AUC performed any better as a predictor of outcome than simply using the administered dose value.

Figure 19 below shows the summary of week 12 response scores for question 3 by dose and by treatment. These figures show that all doses were superior to placebo.

The analyses showed that three covariates appear to influence the baseline value. There was a 12% decrease in baseline for each decade increase in age, a 3% decrease for every 10-kg increase, and a 17% increase for subjects with psychogenic etiology.

¹. How often were you able to penetrate your partner?

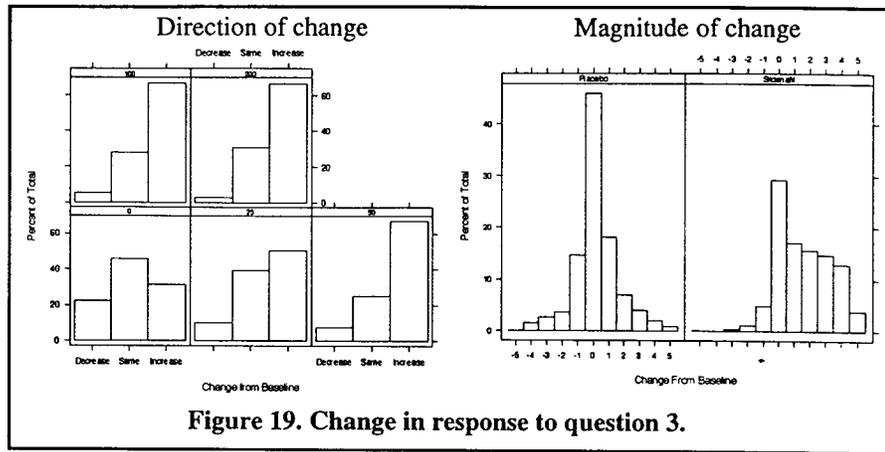


Figure 19. Change in response to question 3.

Table 54. Effect of additive or proportional E_{max} and estimation method on fit to pharmacodynamic model.

	Objective function			
	1st order		1st order conditional	
	Add	Prop	Add	Prop
Dose	7894	8022	7621	8150
Sildenafil AUC	7905	8025	7648	8221
UK-103,320 AUC	7909	8026	7665	8156

No significant covariate relationships could be discerned for E_{50} . Table 55 below shows the results of fitting the final covariate model to a series of datasets with one of the five datasets sequentially removed and replaced.

Table 55. Effect of deletion of studies from final pharmacodynamic model^a.

	Study deleted							Study deleted					
	None	-364	-106	-104	-103	-102		None	-364	-106	-104	-103	-102
Base	1	1.13	0.90	0.98	1.03	—	Add	1	1.11	1.09	1.02	1.04	—
D_{50} ^b	1	1.14	1.00	0.83	1.10	—	Age	1	1.04	0.98	1.02	1.08	0.86
Placebo	1	1.04	0.83	1.13	1.02	—	Subject	1	0.97	1.11	0.83	0.99	1.08
Pcbo ETA ^c	1	0.91	0.91	1.06	1.01	—	Weight	1	1.16	0.95	0.56	0.86	1.52

a. For question 3, how often were you able to penetrate your partner?

b. Dose producing half-maximal response.

c. No idea

For a patient of average age and weight, and with organic etiology for sexual dysfunction, the mean baseline value was 1.51, E_{max} was 5, the mean±SE D_{50} was estimated to be 36±6 mg, and the placebo response was 0.45±0.08. As these components were modeled in an additive manner, the average maximum drug response was 3.05. The inter-individual variability on E_{50} was estimated to be 331±11% and on placebo 148±31%. The level of additive residual variability (SD±SE) was estimated to be 0.46±17%. Figure 20 below gives the results of the simulation that the sponsor performed over a dosing range from 0 to 200 mg.

Table 56 below gives the estimated D_{50} (mg) for each of the five clinical studies used in the population model. These results suggest that subjects in study 104, who were

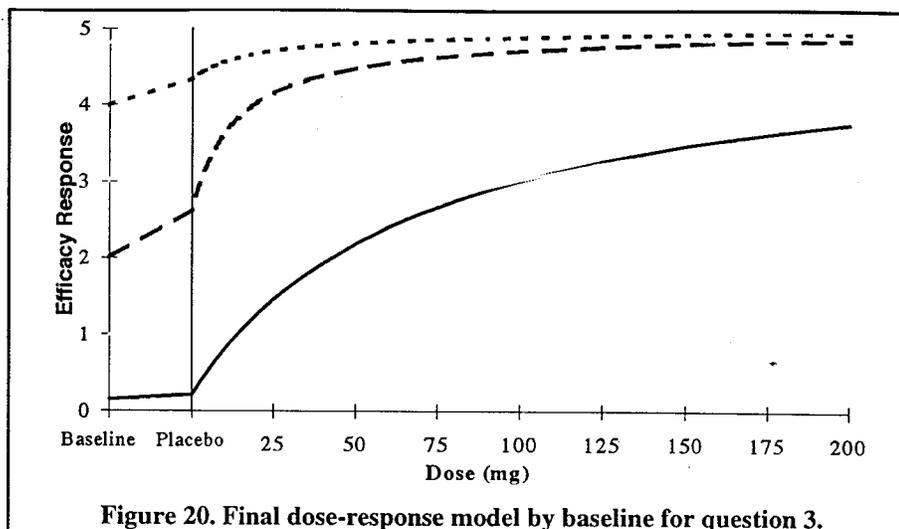


Figure 20. Final dose-response model by baseline for question 3.
mostly diabetics, were less responsive to the effects of sildenafil compared to the other subjects.

Table 56. Estimated D₅₀ for question 3, by study.

	148-102	148-103	148-106	148-364	148-104
D ₅₀	26±7.7	20±7.7	40±11	29±7.8	182±67

Effectiveness question 4²: A similar model to that developed for question 3 was used to model the effectiveness scores in response to question 4. Table 57 below gives the results of fitting the final model to a series of data sets with one of the data sets removed and replaced. Similar results to those of question 3 were obtained. There was an 11% decrease in baseline values for each decade increase in age, a 4% decrease for each 10-kg increase in weight, and a 17% increase for psychogenic etiology for sexual dysfunction.

Table 57. Effect of deletion of studies from final pharmacodynamic model^a.

	Study deleted							Study deleted					
	None	-364	-106	-104	-103	-102		None	-364	-106	-104	-103	-102
Base	1	1.09	0.97	1.01	1.01	—	Add	1	1.12	1.09	1.02	1.05	—
D ₅₀ ^b	1	1.08	0.98	0.85	1.13	—	Age	1	1.03	1.05	1.03	1.01	0.83
Placebo	1	1.12	1.07	1.13	1.12	—	Subject	1	0.84	1.06	0.88	0.98	1.21
Pcbo ETA ^c	1	0.90	0.92	1.03	1.01	—	Weight	1	0.99	0.90	0.68	1.15	1.30

- a. For question 4, how often were you able to maintain an erection after penetration?
- b. Dose producing half-maximal response.
- c. No idea

For a subject of average weight and age and with organic etiology, the mean baseline value was 0.9, E_{max} was 5, (mean±SE) E₅₀ was 41±5.6 mg, and the mean placebo response was 0.4±0.07. Therefore, the average maximum drug response was estimated to be 3.7. The inter-individual variability on E₅₀ was 316±15% on active treatment and 119±31% on placebo. The level of additive variability (SD±SE) was 0.5±20%.

². How often were you able to maintain an erection after penetration?

Table 58 below gives the estimated D₅₀ (mg) for each of the five clinical studies used in the population model.

Table 58. Estimated D₅₀ for question 4, by study.

	148-102	148-103	148-106	148-364	148-104
D ₅₀	28±6.7	22±7.6	49±12	35±8.3	199±66

These results confirm the findings of the responses to question 3, that the drug seems to be less effective in diabetic subjects. Similarly, Figure 21 below shows the summary of week 12 response scores for question 4 by dose and by treatment. These figures confirm the previous finding that all doses were superior to placebo. Figure 18 gives the results of the simulation that the sponsor performed over a dosing range from 0 to 200 mg.

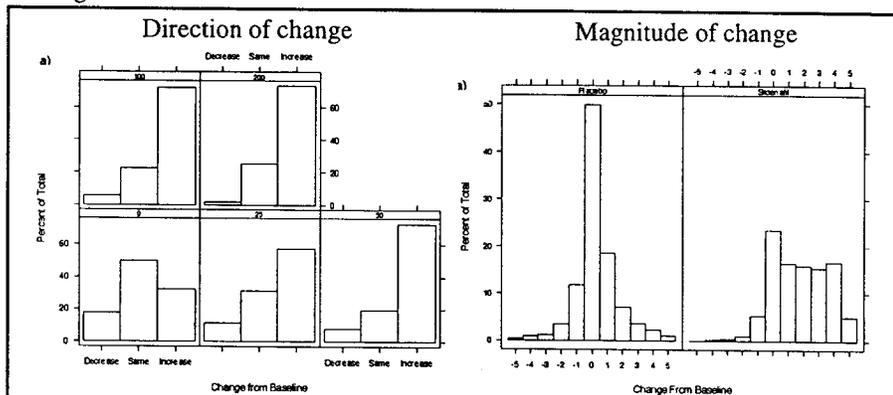


Figure 21. Change in response to question 4.

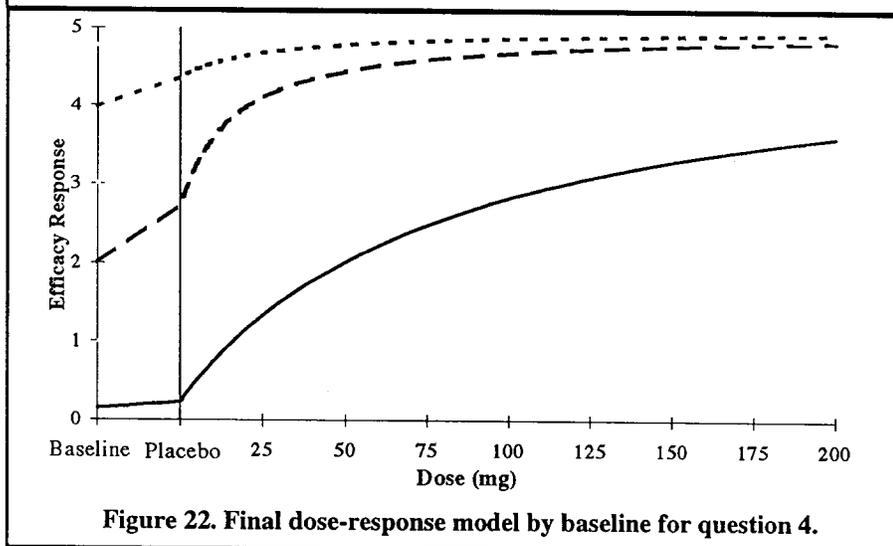
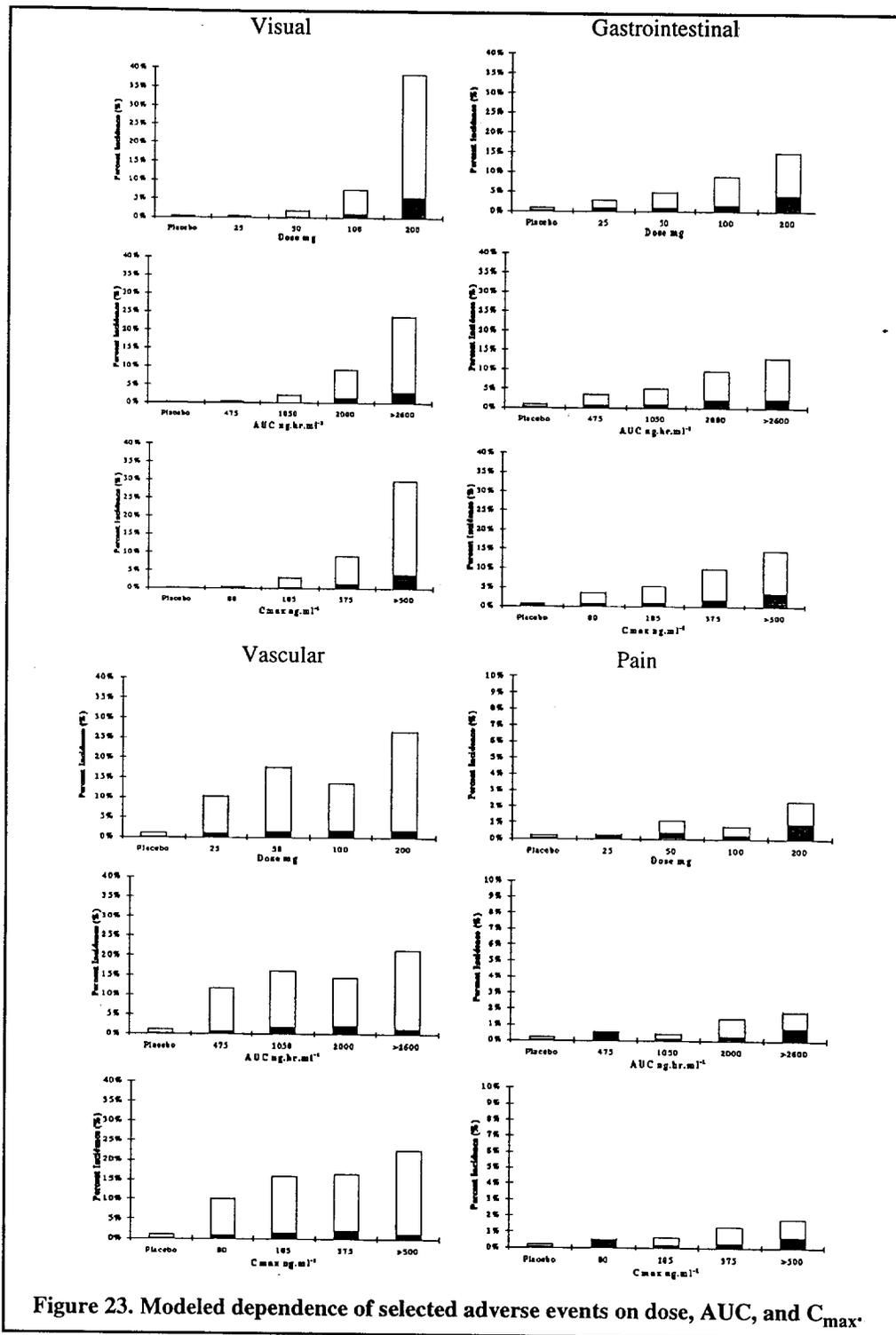


Figure 22. Final dose-response model by baseline for question 4.

A2.2.4. Adverse events

Figure 23 below shows the modeled incidence of specific classes of adverse events by severity (solid bars show moderate or severe events). The incidences of visual, gastrointestinal, vascular, and pain adverse events are all shown to be related to dose, drug AUC, and C_{max}. As with the efficacy analysis, it seems that relationships to dose appear to be as predictive as drug AUC or C_{max}. The incidence of adverse events rose steeply in association with doses of 200 mg, AUC >2600 ng.h/mL, or C_{max} >500 ng/mL. At this highest exposure level, the modeled incidence of abnormal vision was 40%, the incidence of gastrointestinal events was 15%, and the incidence of vascular events was about 25%.



A2.3. Summary

This population analysis showed that hepatic transaminase elevation, aging, and the concomitant administration of CYP3A4 inhibitors can each reduce the clearance of sildenafil. Hepatic transaminase elevation and co-administration of loop diuretics and nonspecific β -blockers were associated with reduced clearance (CL/F) for the metabolite UK-103,320. Increased weight was associated with increased volume of distribution of both sildenafil and its metabolite.

Population effectiveness analyses showed that the responses to questions 3 and 4 can be described by an E_{\max} model with terms for baseline values and placebo response. Baseline values were affected by age, weight, and etiology of erectile dysfunction. The analyses showed that sildenafil was effective regardless of such factors, but probably less effective in subjects with diabetes mellitus than with other etiologies. Dose was as good a predictor of effectiveness as drug AUC or metabolite AUC.

Population analyses of adverse events showed an increase in the incidence of adverse events at a dose of 200 mg.

A3. Development and validation of the primary efficacy instrument (International Index of Erectile Function; IIEF).

A3.1. Source documents Study report: IND 101 17.1.

A3.2. IIEF development The IIEF questionnaire was developed by the sponsor from a variety of sources including published literature and interviews conducted in multiple countries. A pilot version of the questionnaire was utilized in study 148-353 (n=351). A near-final version was subsequently developed and subjected to a validation program in 10 languages in 12 countries (US and Europe). Minor revisions resulted in the IIEF sexual function scale utilized in the phase III program¹.

A3.3. IIEF validation studies The IIEF was validated based upon data obtained in three clinical studies. Study 148-359² involved 111 subjects with erectile dysfunction studied at baseline and after 4 weeks of treatment and study 148-451³ involved 109 age-matched normal male volunteers studied once.

A "principal components analysis with varimax rotation" and some clinical judgement applied to the data in study 148-359 allowed the 15 questions to be allocated to domains pertaining to erectile function, ejaculatory function, sexual desire, satisfaction with intercourse, and overall satisfaction. Generally questions related well to a single domain ("independent factor structure"). Inter-domain correlations ranged from 0.30 to 0.76.

Comparison of IIEF responses with the independent evaluation of each domain by the clinician allowed assessment whether the IIEF measured what it was supposed to measure ("convergent validity"). Such measures were reported as highly statistically significant. The same study compared results of the IIEF with those of related, but distinctly different, domains: marital adjustment (Locke-Wallace⁴) and social

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- ¹. Study 148-102: A double-blind, randomized, placebo-controlled, parallel group, fixed-dose, multicenter study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction. on page 104, Study 148-103: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male patients with erectile dysfunction. on page 111, Study 148-104: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male diabetic patients with erectile dysfunction. on page 118, Study 148-106: A double-blind, randomised, placebo controlled, parallel group, multicentre, fixed-dose study to assess the efficacy and safety of sildenafil administered as required to male subjects with erectile dysfunction. on page 126, Study 148-363: A double-blind, randomised, placebo-controlled, parallel group, multi-centre, flexible dose escalation study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction. on page 206, Study 148-364: A double-blind, randomised, placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of fixed doses of sildenafil administered for three months to male patients with erectile dysfunction. on page 212, and Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord. on page 218.
 - ². Study 148-359: A 12 week, double blind, placebo controlled, parallel group, multicentre study to evaluate a new sexual function questionnaire in the assessment of the efficacy of sildenafil (UK-92,480) in patients with erectile dysfunction. on page 199.
 - ³. Study 148-451, "A study to generate sexual function and quality of life data in male subjects who do not have a diagnosis of erectile dysfunction" was conducted at 3 sites in the UK between February 1996 and July 1996. Subjects (n=109) who were normal, age-match controls for subjects in study 148-359 received no treatment; they merely filled out the IIEF and quality of life questionnaires.
 - ⁴. This is a 15-question survey with defined point-values for various responses. Higher values indicate a harmonious relationship. Reference is Journal of Consulting Psychology (1960) 24:349-354.

desirability (Marlowe-Crowne⁵). For these, the correlations were poor and not statistically significant (“divergent validity”).

Large and highly statistically significant differences were seen between the responses of subjects with the presumed condition (study 148-359) and normal volunteers (study 148-451), indicating that the IIEF reliably distinguishes subjects with erectile dysfunction (“discriminant validity”).

Subjects in study 148-359 self-rated as treatment responders showed large and statistically significant improvements from baseline in each domain (“sensitivity”), while subjects self-rated as non-responders showed no significant changes in scores (“specificity”).

Study 148-401⁶ used the final version of the IIEF as a 4-week study in 37 subjects with erectile dysfunction and 21 age-matched control subjects. Both groups were evaluated using the IIEF, at baseline and after 4 weeks (no treatment). Pearson product-moment correlation coefficients, by domain, ranged from 0.64 to 0.84, indicating a relatively high reproducibility (“test-retest repeatability”).

All three studies evaluated the correlation among questions within a domain using Cronbach’s alpha. Values ranged from 0.73 to 0.96, indicative of highly consistent responses (“internal consistency”).

⁵ This is a 33-true/false question survey of personal attitudes on social issues. Reference is *Marriage and Family Living* (1959) 21:251-255.

⁶ Study 148-401, “A psychometric validation of the International Index of Erectile Function (IIEF) in male patients with erectile dysfunction and age-matched controls” was conducted between February and May 1996 at one site in the US. Subjects with erectile dysfunction (n=37) or normal volunteers (n=21) completed surveys at baseline and 4 weeks later. There was no study treatment.

A4. Study 148-001: Phase I single dose, open study of the clinical pharmacology of sildenafil in elderly and young healthy male volunteers.

- A4.1. Source documents** Study protocol NDA 20-895, vol 1.39; study report: NDA vol 1.39; electronic document: 46917384.pdf.
- A4.2. Investigators**
- A4.3. Study dates** 9 January 1995 to 2 February 1995.
- A4.4. Study design** This study description was based upon the final study report, dated 2 June 1997.
- A4.4.1. Objectives** The objectives were
- To assess the side effect and laboratory test safety profile of a single dose of sildenafil in elderly males (age 65 years or older) and young males (age 18 to 45 years inclusive).
 - To compare the disposition of a single dose of sildenafil administered orally between elderly and young male subjects.
- A4.4.2. Formulation** Drug supplies were 25-mg capsules, lot ED-S-347-994.
- A4.4.3. Population** The intent was to enroll 15 young normal male volunteers, age 18 to 45, and 15 elderly male volunteers, age >65.
- A4.4.4. Procedures** This was an open, parallel, single-dose study in 15 young and 15 elderly male volunteers. In the morning, following an overnight fast, each subject received sildenafil 50 mg with 240 ml of water. During each treatment period, 3-ml blood samples were collected at the following times: 0, 0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40, and 48 hours post-dose.
- A4.4.5. Assay**
- A4.4.6. Analysis** Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Confidence intervals were calculated on the ratios of the log-transformed C_{max} and AUC for the 2 age groups. Untransformed AUC for sildenafil and its metabolite was subjected to regression analysis to determine whether there was a linear relationship between AUC and age or creatinine clearance that would explain any changes in AUC. Two regression models were fitted using type I sums of squares. The first analysis tested if creatinine clearance alone significantly influenced variability in AUC and if age (age/Clcr) significantly further influenced variability in AUC. In the second analysis, age was fitted first followed by creatinine clearance. This analysis tested if age alone significantly influenced variability in AUC and if creatinine clearance (Clcr/age) significantly further influenced variability in AUC.
- A4.4.7. Safety** Routine safety data were recorded.
- A4.5. Results**
- A4.5.1. Conduct** All 30 subjects completed both study phases. Protocol violations appear to have been minor.
- A4.5.2. Pharmacokinetics** Mean plasma concentration-time profiles for sildenafil and its metabolite for elderly and young subjects are shown in Figure 24 below. The corresponding parameters summarized in Table 59 below. Figure 25 below shows relationships among selected pharmacokinetic parameters for young and elderly subjects. The left side of Figure 25.

shows, for sildenafil, AUC as a function of age, Cl/F as a function of creatinine clearance, and C_{max} as a function of age. The right side of Figure 25. shows, for metabolite UK-103,320, AUC as a function of age, AUC as a function of creatinine clearance, and C_{max} as a function of age.

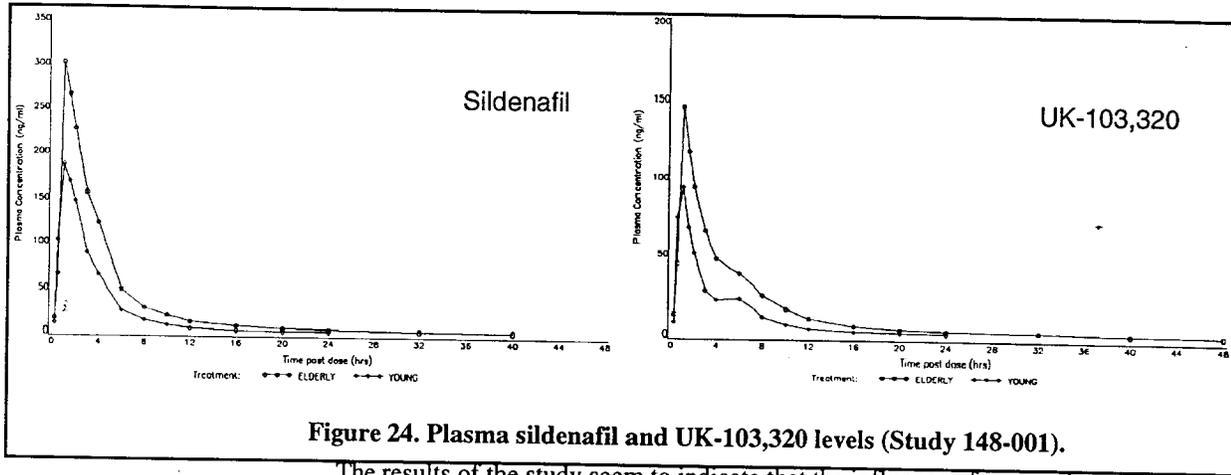


Figure 24. Plasma sildenafil and UK-103,320 levels (Study 148-001).

The results of the study seem to indicate that the influence of age on the pharmacokinetics of sildenafil and its metabolite is marked, since elderly subjects showed almost doubling in their AUC and C_{max} . This difference in plasma levels could be partially attributable to differences in oral clearance. Moreover, the fraction of unbound drug was smaller in the elderly compared to the young (3.4 vs. 4.3%), and this difference in protein binding might result in differences in volume of distribution leading to elevated plasma levels in the elderly compared to the young. The relationships between AUC and age for both sildenafil and its metabolite were not attributable to age-related differences in creatinine clearance. Inclusion of age and creatinine clearance in the regression model showed that the effect of age was statistically significant ($p=0.0055$), but the effect of creatinine clearance was not ($p=0.93$).

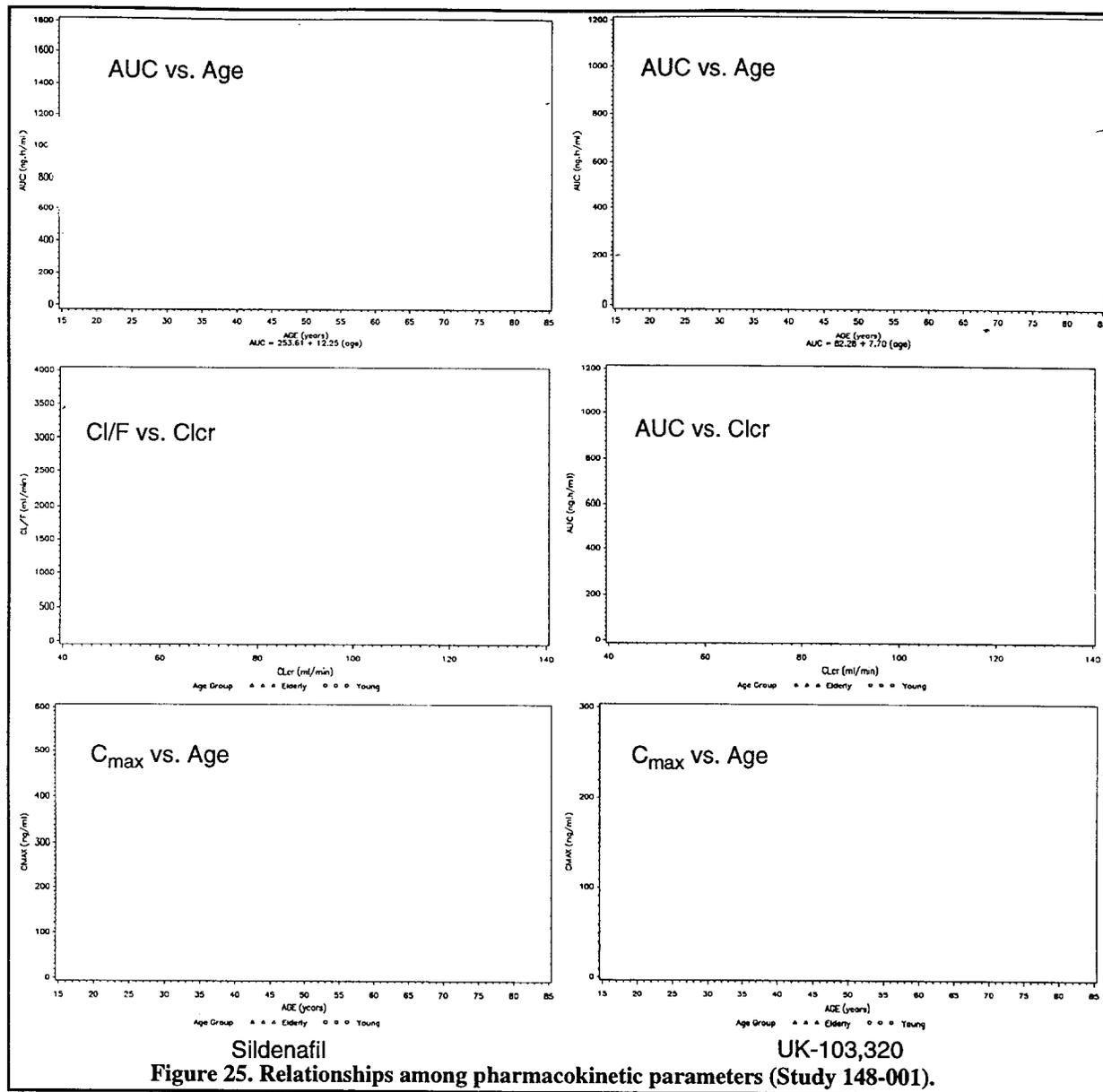


Table 59. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-001).

	Sildenafil		UK-103,320			Sildenafil		UK-103,320	
	Young	Elderly	Young	Elderly		Young	Elderly	Young	Elderly
C _{max} (ng/mL)	178	303	90	146	t _{1/2} (h)	2.6	3.8	3.1	5.2
T _{max} (h)	1.1	1.2	0.9	1.0	Unbound (%)	4.3	3.4	4.9	3.8
AUC (ng·h/mL)	586	1077	282	582	Cl/F (mL/min)	1537	800	—	—
k _{el} (h ⁻¹)	0.27	0.18	0.2	0.13					

A4.5.3. Safety

There were no serious or severe adverse events reported.

A4.6. Summary

The results of the study showed that elderly subjects had about twice as high AUC and C_{max} for sildenafil and metabolite UK-103,320 compared to young subjects. The difference was not attributable to differences in creatinine clearance.