Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Appendix A23, page 150 through Appendix A33.6, page 169

Study 148-216: An open study to investigate the effects of a single dose of UK-   *NDA 20-895*
92,480 (50mg) on bleeding time, followed by a double-blind, placebo-controlled,   *Sildenafil for male impotence*
two-way crossover study to investigate the effects of a single dose of UK-92,480

A23. Study 148-216: An open study to investigate the effects of a single dose of UK-92,480 (50mg) on bleeding time, followed by a double-blind, placebo-controlled, two-way crossover study to investigate the effects of a single dose of UK-92,480 (50mg) on aspirin-induced prolongation of bleeding time in healthy male volunteers.

A23.1. Source documents

Study protocol NDA 20-895, vol 1.61; study report: NDA vol 1.61; electronic document: 47153405.pdf.

A23.2. Investigators

Single-center study with 1 investigator in the UK.

A23.3. Study dates

17 October 1994 to 20 December 1994.

A23.4. Study design

This study description was based upon the final study report, dated 20 September 1996.

A total of 18 health male volunteers, age 18 to 45, were to be recruited.

There were two study phases. The first phase was an open study in which subjects received a single dose of sildenafil 50 mg. The second phase was a double-blind crossover study in which subjects received aspirin 150 mg qd for 7 days and, in random order, placebo and sildenafil on days 4 and 7. Bleeding time was assessed by the 'simplate technique' prior to dosing with study drug and then at 1 and 4 hours after dosing.

Routine safety data were recorded.

A23.5. Results

A23.5.1. Conduct

Eighteen subjects were randomized and completed both study phases. There were minor protocol deviations, but no subject was excluded from analyses.

A23.5.2. Pharmacodynamics

Bleeding time data are shown in Table 110 below, as analyzed by the sponsor. The 4-hour data were not analyzed. The 95% confidence limits on the ratio of bleeding time on aspirin plus sildenafil to bleeding time on aspirin plus placebo were 89 to 128%.

Table 110. Bleeding time (Study 148-216).

	Baseline	1 hour
Sildenafil alone (min±SD)	8.2±3.9	7.2±2.9
Aspirin + placebo	11.0±3.9	12.9±5.6
Aspirin + sildenafil	10.7±4.1	14.7±8.8

Although mean effects were not statistically significant, 3 subjects had bleeding times doubled one hour after aspirin + sildenafil compared with aspirin + placebo.

A23.5.3. Safety

There were no serious or treatment-related severe adverse reactions.

A23.6. Summary

Despite the lack of a statistically significant treatment effect, sildenafil probably does produce prolonged bleeding times in some individuals receiving aspirin.

Study 148-217: A double blind, randomised, placebo controlled, three way   *NDA 20-895*
crossover study to investigate the haemodynamic and pharmacokinetic interactions   *Sildenafil for male impotence*
of sildenafil and alcohol in healthy male volunteers.

A24. Study 148-217: A double blind, randomised, placebo controlled, three way crossover study to investigate the haemodynamic and pharmacokinetic interactions of sildenafil and alcohol in healthy male volunteers.

A24.1. Source documents

Study protocol NDA 20-895, vol 1.62; study report: NDA vol 1.62; electronic document: 47151059.pdf.

A24.2. Investigators

Dr. MD Eve, Pfizer Clinical Research Unit, Kent and Canterbury Hospital, Ethelbert Road, Canterbury CT1 3NG England.

A24.3. Study dates

2 November 1994 to 21 December 1994.

A24.4. Study design

This study description was based upon the final study report, dated 22 August 1997.

A24.4.1. Objectives

The objectives were
- To study the hemodynamic effects of sildenafil when taken with alcohol.
- To characterize any pharmacokinetic interaction between sildenafil and alcohol.
- To examine the safety and toleration of a single dose of sildenafil when taken acutely with alcohol.

A24.4.2. Formulation

Sildenafil was to be supplied 25-mg capsules (lot #979-12). Matching placebo capsules were from lot #748-43. Absolute ethanol was from lot #L-435402. Placebo alcohol was orange juice and two drops of absolute ethanol.

A24.4.3. Population

Twelve healthy male subjects between 18 and 45 years were to be recruited.

A24.4.4. Procedures

The study was a double blind, randomised, placebo controlled, 3-way crossover study in which subjects received, in random order, sildenafil 50 mg alone, 0.5 g/kg of alcohol alone, and sildenafil plus alcohol together. There was a minimum of a 7 day washout period between treatments. The alcohol was diluted to 200 ml with orange juice. The contents were drunk in 2 minutes or less. For sildenafil and metabolite measurement, plasma samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. For alcohol determination, plasma samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post-dose.

A24.4.5. Assay

A24.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Pair-wise comparisons were made between the sildenafil plus alcohol group and the sildenafil group using a t-test, where the estimate of variability was obtained from ANOVA. Ninety-five percent confidence intervals were also constructed for the parameters of interest.

A24.4.7. Safety

Routine safety data were recorded.

A24.5. Results

A24.5.1. Pharmacokinetics

Mean plasma concentration time profiles for sildenafil and its metabolite with and without alcohol are shown in Figure 49 below, while the corresponding parameters are

Study 148-217: A double blind, randomised, placebo controlled, three way   NDA 20-895
crossover study to investigate the haemodynamic and pharmacokinetic interactions   *Sildenafil for male impotence*
of sildenafil and alcohol in healthy male volunteers.

summarized in Table 111 below, along with 95% confidence limits for the comparison of sildenafil alone to sildenafil plus ethanol. Figure 50 below shows the mean ethanol plasma concentration vs. time profile with and without sildenafil.
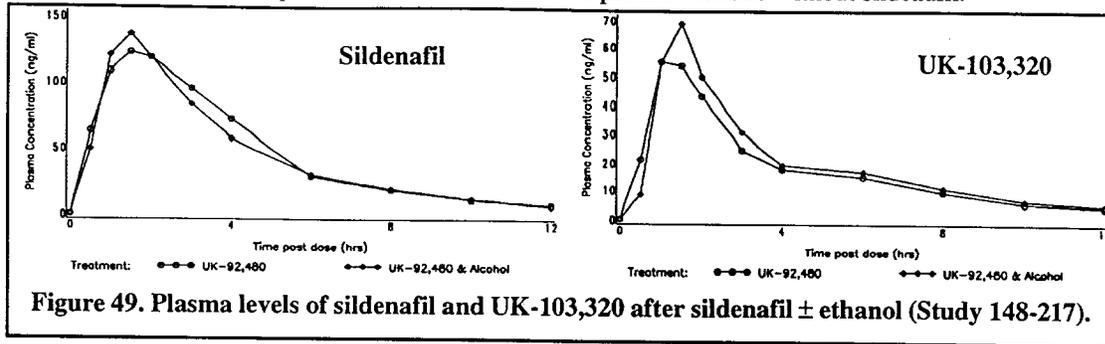

Figure 49. Plasma levels of sildenafil and UK-103,320 after sildenafil ± ethanol (Study 148-217).

Table 111. Pharmacokinetic parameters for sildenafil, UK-103,320, and ethanol (Study 148-217).

	Sildenafil			UK-103,320			Ethanol[a]		
	Sil only	Sil+EtOH	Ratio or Δ^b (95% CI)	Sil only	Sil+EtOH	Ratio or Δ (95% CI)	Sil only	Sil+EtOH	Ratio or Δ (95% CI)
AUC (ng.h/mL)	552	542	0.77 - 1.26	224	542	0.96 - 1.34	195	542	0.98 - 1.30
C_{max} (ng/mL)	145	157	0.75 - 1.57	58	157	0.96 - 1.71	80	157	0.97 - 1.35
T_{max} (h)	1.6	1.4	-0.68 - 0.35	1.5	1.4	-0.53 - 0.37	0.7	1.4	-0.40 - 0.06
k_{el} (h^{-1})	0.23	0.23	-0.03 - 0.04	0.18	0.23	-0.05 - 0.05	—	0.23	—
$t_{1/2}$ (h)	3.0	3.0	—	3.9	3.0	—	—	3.0	—

a. For ethanol, AUC is in mg.h/dL and C_{max} is mg/dL.
b. (Sildenafil+EtOH)/(Sildenafil) for AUC and C_{max}; (Sildenafil+EtOH)-(Sildenafil) for T_{max} and k_{el}.
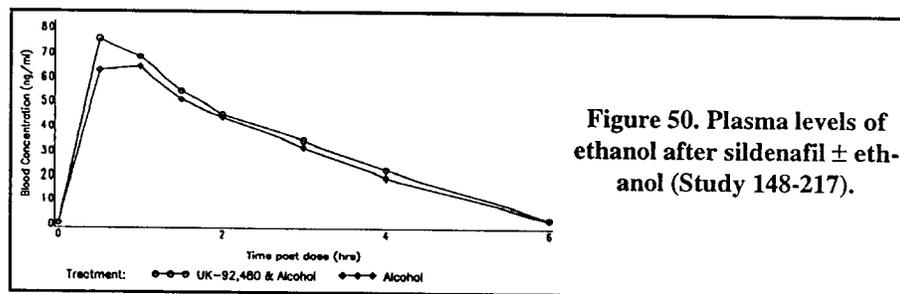

Figure 50. Plasma levels of ethanol after sildenafil ± ethanol (Study 148-217).

The results of the study show that there in general there was a slight increase in the metabolite concentrations with the co-administration of ethanol. AUC increased by 13% and C_{max} by 28%. However, the increase in these pharmacokinetic parameters did not achieve statistical significance. A statistically insignificant increase in the ethanol plasma concentrations was observed with the co-administration of sildenafil; C_{max} and AUC increased by 13 and 15%, respectively.

A24.5.2. Safety

There were no serious or severe adverse events. Common events—headache, penile erection, and vasodilation—had a similar incidence on sildenafil alone and sildenafil plus ethanol.

A24.6. Summary

The results of the study showed that co-administration sildenafil with ethanol did not result in any clinically significant alterations of the pharmacokinetics of either sildenafil or ethanol.

Study 148-218: A double blind, randomised, placebo controlled, two-way crossover   *NDA 20-895*
study to investigate any pharmacokinetic or pharmacodynamic interaction between   *Sildenafil for male impotence*
orally administered UK-92,480 and tolbutamide in healthy male volunteers.

A25. Study 148-218: A double blind, randomised, placebo controlled, two-way crossover study to investigate any pharmacokinetic or pharmacodynamic interaction between orally administered UK-92,480 and tolbutamide in healthy male volunteers.

A25.1. Source documents	Study protocol NDA 20-895, vol 1.63; study report: NDA vol 1.63; electronic document: 47150192.pdf.
A25.2. Investigators	Dr M D Eve, Pfizer Clinical Research Unit, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent, United Kingdom.
A25.3. Study dates	18 January 1995 to 6 April 1995.
A25.4. Study design	This study description was based upon the final study report, dated 2 December 1996.

A25.4.1. Objectives

The objectives were
- To characterize any pharmacokinetic interaction between oral doses of sildenafil and tolbutamide.
- To characterize any pharmacodynamic interaction between oral doses of sildenafil and tolbutamide by measuring plasma glucose concentrations.
- To assess the safety and toleration of a single dose of sildenafil when taken concomitantly with tolbutamide.

A25.4.2. Formulation

Drug supplies are shown in Table 112 below.

Table 112. Drug supplies (Study 148-218).

	Lot		Lot
Tolbutamide 500 mg	3818-033A 3818-033B	Placebo for sildenafil	748-43
		Sildenafil 25 mg capsules	979-12

A25.4.3. Population

A total of 12 health male volunteers, age 18 to 45, were to be recruited.

A25.4.4. Procedures

In random order and separated by 7 days, subjects received single oral doses of tolbutamide 250 mg accompanied by placebo or sildenafil 50 mg.

Blood glucose levels were to be assessed pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing.

Blood samples for determination of plasma levels of tolbutamide were obtained pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 hours post-dose. Samples were collected in heparinized tubes, plasma was separated by centrifugation, and samples were stored at -20°C.

Urine was collected for assay of hydroxytolbutamide and carboxytolbutamide in intervals 0-12 and 12-24 hours after dosing.

A25.4.5. Assay

A25.4.6. Analysis

C_{max}, AUC_{τ}, k_{el}, AUC, T_{max}, and $t_{1/2}$ were calculated. In addition, the ratio of urinary metabolites was assessed.

A25.4.7. Safety

Routine safety data were recorded.

A25.5. Results

A25.5.1. Conduct

Twelve subjects were randomized and treated. Eleven of 12 subjects broke fast for treatment of hypoglycemia, so blood glucose data were not analyzed. Other protocol violations appear to have been minor.

Study 148-218: A double blind, randomised, placebo controlled, two-way crossover study to investigate any pharmacokinetic or pharmacodynamic interaction between orally administered UK-92,480 and tolbutamide in healthy male volunteers.

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A25.5.2. Pharmacokinetics

Plasma levels of sildenafil and UK-103,320 are shown in Figure 51 below. Pharmacokinetic parameters are shown in Table 113 below.
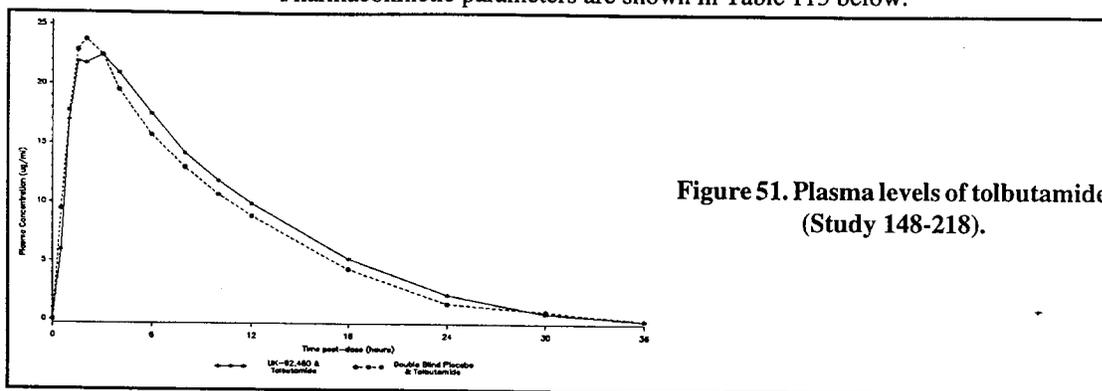

Figure 51. Plasma levels of tolbutamide (Study 148-218).

Table 113. Pharmacokinetic parameters for tolbutamide (Study 148-218).

	Placebo	Sildenafil		Placebo	Sildenafil
AUC_t (µg.h/mL)	231±65	247±71	T_{max} (h)	1.8±0.7	2.2±1.0
AUC (µg.h/mL)	266±69	285±74	K_{el} (h^{-1})	0.11±0.02	0.10±0.02
C_{max} (µg/mL)	24.7±2.7	24.8±4.0	$t_{1/2}$ (h)	6.6	6.8

Excretion of metabolites of tolbutamide is characterized in Table 114 below.

Table 114. Urinary excretion of tolbutamide metabolites (Study 148-218).

	Carboxytolbutamide		Hydroxytolbutamide		Carboxy:hydroxy	
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
0-12 hours	105±23	115±35	20±6.3	22±6.6	5.8±3.1	5.4±2.3
12-24 hours	43±5.5	44±12	7.0±1.7	7.2±2.2	6.7±3.0	6.1±0.9

A25.5.3. Safety

Other than hypoglycemia, the only common adverse event was headache. Two subjects reported erections. One subject reported visual disturbances.

A25.6. Summary

Sildenafil inhibits CYP2C9 activity in vitro. CYP2C9 is involved in metabolism of tolbutamide, an oral hypoglycemic agent, so a potentially important drug interaction was possible. However, plasma levels of tolbutamide and urinary excretion of its metabolites were unaffected by single oral doses of sildenafil 50 mg. The study appears to have been powered adequately to detect a 30% change in AUC or C_{max}, but single doses of sildenafil below the maximum recommended dose was not the optimum study design.

*Study 148-219: A double-blind, randomised, placebo-controlled, two-way
crossover study to assess the potential interaction between orally administered UK-
92,480 (sildenafil) and warfarin in healthy male volunteers.*

*NDA 20-895
Sildenafil for male impotence*

A26. Study 148-219: A double-blind, randomised, placebo-controlled, two-way crossover study to assess the potential interaction between orally administered UK-92,480 (sildenafil) and warfarin in healthy male volunteers.

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A26.1. Source documents	Study protocol NDA 20-895, vol 1.64; study report: NDA vol 1.64; electronic document: 47152646.pdf.
A26.2. Investigators	Dr D Kleinermans, Hôpital Erasme, Pfizer Clinical Research Unit, 808 Route de Lennik, 1070 Bruxelles, Belgium.
A26.3. Study dates	26 January to 3 March 1995.
A26.4. Study design	This study description was based upon the final study report, dated 10 December 1996.
A26.4.1. Objectives	The objective was to examine the safety, toleration and hemostatic effects (bleeding time and prothrombin time) of oral sildenafil taken concomitantly with warfarin.
A26.4.2. Formulation	Drug supplies are shown in Table 115 below.

Table 115. Drug supplies (Study 148-219).

	Lot		Lot
Warfarin 40 mg	—	Placebo for sildenafil	748-43
		Sildenafil 25 mg capsules	3039-134

A26.4.3. Population	A total of 12 health male volunteers, age 18 to 45, were to be recruited.
A26.4.4. Procedures	In random order and separated by 4 days, subjects received oral doses of placebo or sildenafil 50 mg in the evenings for 6 days. Subjects took an additional dose of placebo or sildenafil on the morning of day 2 accompanied by a single oral dose of warfarin 40 mg.
	Blood samples for prothrombin time were obtained prior to the first dose of placebo or sildenafil, prior to administration of warfarin, and then at 4, 8, 12, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dosing. Bleeding time was assessed prior to the first dose of placebo or sildenafil and then 38 hours after administration of warfarin.
A26.4.5. Assay	Prothrombin time was assessed by standard methods.
A26.4.6. Safety	Routine safety data were recorded.

A26.5. Results

A26.5.1. Conduct	Twelve subjects were randomized and treated. Protocol violations appear to have been minor.
A26.5.2. Pharmacodynamics	Individual prothrombin time profiles are shown in Figure 52 below. Mean bleeding times and prothrombin times are shown in Table 116 below. The sponsor's analysis of AUEC[1] for prothrombin time showed a statistically significant difference between treatment groups.

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[1] Area under the effect curve.

Study 148-219: A double-blind, randomised, placebo-controlled, two-way
crossover study to assess the potential interaction between orally administered UK-
92,480 (sildenafil) and warfarin in healthy male volunteers.

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Sildenafil for male impotence

Table 116. Bleeding time and prothrombin time (Study 148-219).

Bleeding time (sec±SD)			Prothrombin time		
	Placebo	Sildenafil		Placebo	Sildenafil
Baseline	343±114	332±86	Baseline (sec±SD)	13.5±0.8	13.6±0.8
On treatment	367±85	378±88	AUEC (sec.h±SD)	3006±667	2895±460
			MaxΔ (sec±SD)	15.6±9.2	14.4±7.3
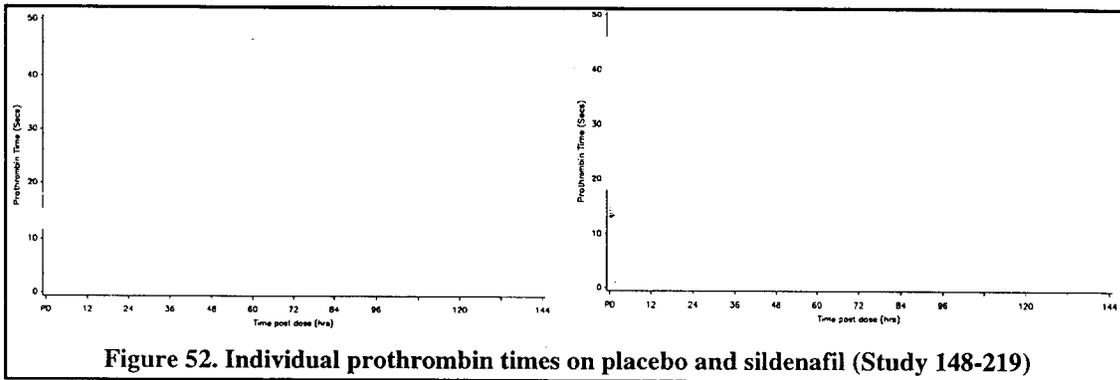
Figure 52. Individual prothrombin times on placebo and sildenafil (Study 148-219)

A26.6. Summary

Oxidation by CYP2C9 is thought to be the principal path of elimination for warfarin. Sildenafil inhibits CYP2C9 activity in vitro and sildenafil inhibits platelet aggregation. Both effects of sildenafil could result in increased bleeding times in patients receiving both drugs. The study design was sub-optimum in utilizing a dose of sildenafil (50 mg) less than the sponsor's recommended maximum. A reduction in the effect of warfarin was evidenced by a statistically significant but clinically meaningless decrease in AUEC; this unexpected result is most likely spurious.

Study 148-221: An open, single dose study to compare the pharmacokinetics, safety
and toleration of a single oral dose of sildenafil in patients with chronic stable
hepatic cirrhosis to healthy subjects with normal hepatic function.

NDA 20-895
Sildenafil for male impotence

A27. Study 148-221: An open, single dose study to compare the pharmacokinetics, safety and toleration of a single oral dose of sildenafil in patients with chronic stable hepatic cirrhosis to healthy subjects with normal hepatic function.

A27.1. Source documents

Study protocol NDA 20-895, vol 1.66; study report: NDA vol 1.66; electronic document: 47053746.pdf.

A27.2. Investigators

A27.3. Study dates

20 December 1995 to 27 February 1996.

A27.4. Study design

This study description was based upon the final study report, dated 14 May 1997.

A27.4.1. Objectives

The objectives were
- To determine the pharmacokinetics of sildenafil and the metabolite UK-103,320 following single oral doses in subjects with chronic stable hepatic cirrhosis and to compare them with those for age and weight matched normal subjects.
- To assess the safety and toleration of a single 50-mg dose of sildenafil in subjects with chronic stable hepatic cirrhosis.

A27.4.2. Formulation

Sildenafil was supplied as 50-mg capsules (lot 3039-135).

A27.4.3. Population

Twelve healthy male subjects between 18 and 70 years were to be recruited to match age (±5 years) and weight (±10 kg) of 12 subjects with chronic stable hepatic cirrhosis. The diagnosis of cirrhosis was to include previous liver biopsy with laboratory and clinical findings supporting cirrhosis. Six (±2) of the subjects with cirrhosis were to conform to the Child-Pugh classification A and 6±2 to the Child-Pugh classification B.

A27.4.4. Procedures

The study was an open, single oral dose, parallel group study. Subjects were given a standard light breakfast on the morning of dosing. Breakfast was completed at least 2 hours before dosing. Blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 6, 10, 18, 24, 36, and 48 hours post-dosing.

A27.4.5. Assay

A27.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Paired tests were used (equivalent to a two-way analysis of variance). AUC and C_{max} were log-transformed before analysis. Mean differences and 95% confidence intervals were calculated on the log scale and then back-transformed to give the ratio and confidence intervals as percentages.

A27.4.7. Safety

Routine safety data were recorded.

A27.5. Results

A27.5.1. Pharmacokinetics

Mean plasma concentration time profiles for sildenafil and its metabolite for the normal and cirrhotic subjects are shown in Figure 53 below while the corresponding parameters are summarized in Table 117 below. Figure 54 below shows the ln(AUC) as a function of the Child-Pugh score.
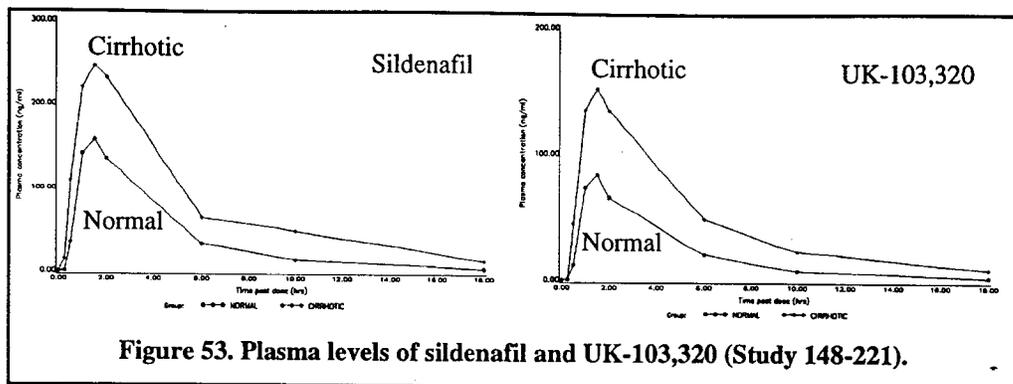
Study 148-221: An open, single dose study to compare the pharmacokinetics, safety and toleration of a single oral dose of sildenafil in patients with chronic stable hepatic cirrhosis to healthy subjects with normal hepatic function.

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Sildenafil for male impotence

Figure 53. Plasma levels of sildenafil and UK-103,320 (Study 148-221).

Table 117. Pharmacokinetic parameters (Study 148-221).

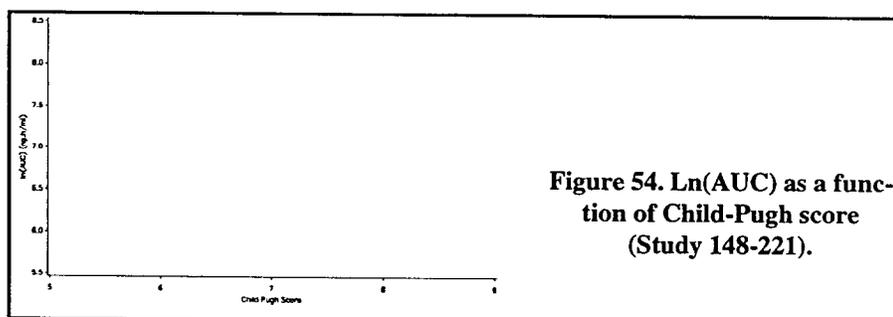|	Sildenafil		UK-103,320			Sildenafil		UK-103,320	
	Normal	Cirrhotic	Normal	Cirrhotic		Normal	Cirrhotic	Normal	Cirrhotic
C_{max} (ng/ml)	155	228	83	155	$t_{1/2}$ (h)	3.2	4.3	3.1	5.8
AUC_τ (ng.h/ml)	664	1225	343	873	CL/f (mL/min)	1255	680	—	—
T_{max} (h)	1.4	1.6	1.3	1.5	Protein binding (% free)	3.5	3.7	4.9	5.6
k_{el} (h^{-1})	0.22	0.16	0.22	0.12					

Figure 54. Ln(AUC) as a function of Child-Pugh score (Study 148-221).

The results of the study show that there was almost doubling of the sildenafil plasma concentrations in the liver impaired subjects. The ratio of geometric AUC means was 185% with a 95% confidence interval of 111 to 307%. The ratio of geometric C_{max} means was 145% with a 95% confidence interval of 97 to 222%. This difference in plasma concentrations can be partially explained by the differences in oral clearance. The cirrhotic patients' oral clearance was 46% lower compared to the healthy volunteers (680 mL/min vs. 1255 mL/min). Analysis of the protein binding revealed no significant difference in free fraction between the two groups, with mean values of 3.5 and 3.7%, respectively. There was no relationship between AUC and the Child-Pugh score.

In view of the above results, one would expect that the concentrations of UK 103,320 would be reduced. However, the results of this study show that plasma levels of the metabolite were doubled in the cirrhotic subjects. The results suggest that the metabolite concentrations are dependent upon the elimination rate and that the intrinsic clearance of the metabolite is affected to a greater extent than is that of the parent drug.

A27.6. Summary

The results of the study showed that in subjects with liver cirrhosis, the plasma levels of sildenafil and its metabolite UK-103,320 were almost double the levels in age- and weight-matched normal controls. This doubling of plasma concentrations might warrant starting such patients on a lower dose of sildenafil.

Study 148-222: Single blind, placebo controlled, parallel group study to investigate the effects of a single oral dose of sildenafil (UK-92,480) (100mg) and isosorbide dinitrate (20mg) on aspirin-induced prolongation of bleeding time in healthy male

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Sildenafil for male impotence

A28. Study 148-222: Single blind, placebo controlled, parallel group study to investigate the effects of a single oral dose of sildenafil (UK-92,480) (100mg) and isosorbide dinitrate (20mg) on aspirin-induced prolongation of bleeding time in healthy male volunteers.

A28.1. Source documents

Study protocol NDA 20-895, vol 1.67; study report: NDA vol 1.67; electronic document: 47147979.pdf.

A28.2. Investigators

Single-center study with 1 investigator in the UK.

A28.3. Study dates

25 August 1995 to 3 November 1995.

A28.4. Study design

This study description was based upon the final study report, dated 21 February 1997.

A total of 36 healthy male volunteers, age 18 to 45, were to be recruited.

This was an investigator-blind, parallel study. Subjects received aspirin 100 mg qd for 4 days and then a single dose of randomized treatment—placebo, ISDN 20 mg, or sildenafil 100 mg. One hour after dosing, blood samples were drawn for plasma levels of sildenafil and UK-103,320. Bleeding times were measured on day 1 and 1 hour after dosing on day 4.

Routine safety data were recorded.

A28.5. Results

A28.5.1. Conduct

Forty-five subjects were randomized and completed both study phases. There were minor protocol deviations, but only one subject was excluded from analyses because of use of aspirin at baseline.

A28.5.2. Pharmacokinetics

One hour after dosing, plasma levels of sildenafil were 124 to 487 ng/mL (mean 298 ng/mL). Plasma levels of UK-103,320 were 43 to 236 ng/mL (mean of 132 ng/mL).

A28.5.3. Pharmacodynamics

Bleeding time data are shown in Table 118 below, as analyzed by the sponsor.

Table 118. Bleeding time (Study 148-222).

	Placebo	ISDN	Sildenafil
Day 1 pre-dose (min±SD)	4.0±0.9	5.5±2.1	4.9±1.2
Day 4 pre-dose	7.6±2.9	11.0±7.5	6.6±1.5
Day 4 hour 1	8.0±2.6	10.5±4.7	8.1±2.1

There were no evident outliers in the sildenafil group.

A28.5.4. Safety

There were no serious or treatment-related severe adverse reactions. The incidence of headache was greater on sildenafil than on placebo, and greater on ISDN than on sildenafil.

A28.6. Summary

Aspirin increased bleeding time, but neither ISDN 20 mg nor sildenafil 100 mg produced further increases in bleeding time 1 hour after dosing.

Study 148-223: A double-blind, randomised, placebo controlled, four period
crossover study to assess the effect of orally administered sildenafil (50, 100 and
200mg) on visual function in healthy male volunteers.

NDA 20-895
Sildenafil for male impotence

A29. Study 148-223: A double-blind, randomised, placebo controlled, four period crossover study to assess the effect of orally administered sildenafil (50, 100 and 200mg) on visual function in healthy male volunteers.

A29.1. Source documents	Study protocol NDA 20-895, vol 1.68; study report: NDA vol 1.68; electronic document: 47111394.pdf.
A29.2. Investigators	Single-center study with 1 investigator in Belgium.
A29.3. Study dates	18 March 1996 to 6 May 1996.
A29.4. Study design	This study description was based upon the final study report, dated 5 August 1997.

A total of 16 health male volunteers, age 40 to 60, were to be recruited. -

This was a double-blind, 4-period crossover study in which subjects received single oral doses of placebo and sildenafil 50, 100, and 200 mg in random order on study days at least 7 days apart. Visual effects were assessed by Snellen charts (visual acuity), Pelli-Robson charts (contrast sensitivity), Farnsworth-Munsell 100-hue tests (color discrimination), and pupillometry performed pre-dose, and 1, 2, 4, 6, and 24 to 36 hours after dosing. Supine vital signs were monitored for 4 hours after dosing.

Blood samples for assay of plasma levels of sildenafil and UK-103,320 were taken pre-dose, and 0.5, 1, 2, 3, 4, 6, 7, and 24 to 36 hours after dosing.

Routine safety data were recorded.

### A29.5. Results

A29.5.1. Conduct	Sixteen subjects were randomized and completed study. There were minor protocol deviations, but no subject was excluded from analyses.
A29.5.2. Pharmacokinetics	C_{max} for sildenafil was 271 ng/mL after a 50-mg dose, increasing dose-proportionally to 1081 ng/mL after a 200-mg dose. The time of the maximum concentration was about 1 hour at all doses. Metabolite UK-103,320 levels were about 40% as high as those for sildenafil. Sildenafil and its metabolite were each about 95% protein-bound.
A29.5.3. Pharmacodynamics	Results of the color discrimination test 1 hour after dosing are shown in Figure 55 below. Pane A shows the change from baseline in the total color discrimination errors as a function of dose. Pane B shows the color distribution of errors in the 200-mg dose group. Treatment effects were not apparent after 4 hours.
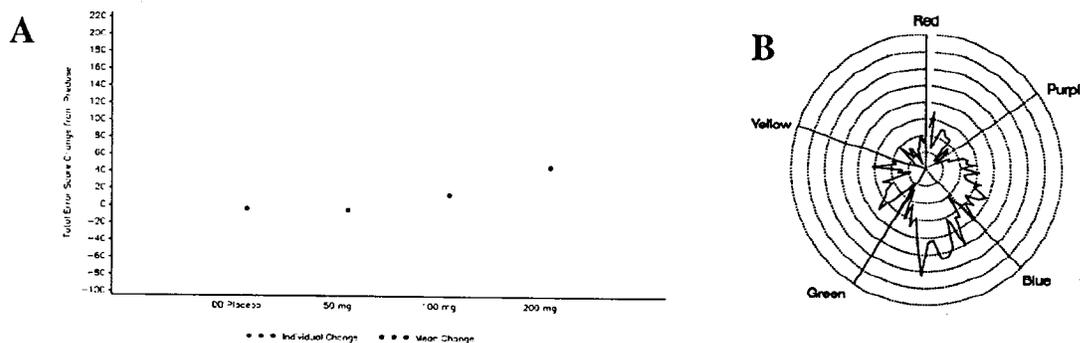
Figure 55. Color discrimination scores (A) by dose and (B) by color at 200 mg (Study 148-223).

In contrast, no apparent treatment effects were observed for tests of contrast sensitivity, visual acuity, or pupillometry.

Study 148-223: A double-blind, randomised, placebo controlled, four period
crossover study to assess the effect of orally administered sildenafil (50, 100 and
200mg) on visual function in healthy male volunteers.

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The main study report makes reference to a PK/PD report, not in evidence. The description of the findings does not indicate whether plasma levels of study drug or metabolite correlate better with color discrimination scores than does dose.

A29.5.4. Safety

There were no serious or treatment-related severe adverse reactions. There was a dose-related increase in the incidence of total adverse events, the most common of which were vasodilation and headache. Other adverse events included visual disturbance

A29.6. Summary

At doses up to 200 mg, the only demonstrated visual effect was impairment of color discrimination. The effect lasted at most a few hours.

Study 148-225: A double-blind, placebo controlled, two way crossover study to   *NDA 20-895*
investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in   *Sildenafil for male impotence*
subjects with essential hypertension being treated with amlodipine.

A30. Study 148-225: A double-blind, placebo controlled, two way crossover study to investigate the effects of a single dose of sildenafil (100 mg) on blood pressure in subjects with essential hypertension being treated with amlodipine.

A30.1. Source documents   Study protocol NDA 20-895, vol 1.70; study report: NDA vol 1.70; electronic document: 47053931.pdf.

A30.2. Investigators   Single-center study with 1 investigator in the United Kingdom.

A30.3. Study dates   7 August 1996 to 24 January 1997.

A30.4. Study design   This study description was based upon the final study report, dated 29 July 1997.

A total of 16 subjects with uncomplicated hypertension treated with a stable dose of amlodipine only, age 18 to 75, were to be recruited.

On each of two clinic days separated by 7 days, subjects received a single oral dose of placebo or sildenafil 100 mg after overnight fast and 2 hours after the usual amlodipine dose. Vital signs and blood samples for assay of plasma levels of amlodipine were taken over the succeeding 8 hours.

Routine safety data were recorded.

A30.5. Results

A30.5.1. Conduct   Sixteen subjects were randomized and completed study. There were minor protocol deviations, but no subject was excluded from analyses.

A30.5.2. Pharmacokinetics   Pharmacokinetic parameters for amlodipine, AUC and C_{max}, were unaffected by sildenafil (with 95% confidence limits of about ±20%). T_{max} for amlodipine did not appear to have been affected either, but the confidence limits there are much wider.

A30.5.3. Pharmacodynamics   The two treatment periods had comparable vital signs at baseline. Effects on vital signs are summarized in Table 119 below. By the sponsor's analyses, most of the treatment group differences were nominally highly statistically significant.

Table 119. Effects on vital signs (Study 148-225).

		Systolic		Diastolic		Heart rate	
		Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
MaxΔ (±SD)	Supine	-8.7±5.4	-17.0±9.7	-2.1±5.4	-7.9±5.2	-0.7±5.1	1.2±4.7
AUC (mmHg.h)		-6.1	-30.0	7.1	-5.5	-19.9	-18.8
MaxΔ (±SD)	Standing	-9.6±7.7	-20.1±13.3	-3.0±4.6	-11.6±11.2	-3.7±4.1	3.7±6.8
AUC (mmHg.h)		-11.2	-35.1	6.8	-16.0	-28.4	-14.5

A30.5.4. Safety   There were no serious or treatment-related severe adverse reactions. Adverse events overall were more common on sildenafil, headache, diarrhea, and penile erections all occurring only on sildenafil. There was one case of postural hypotension (BP fall from 136/76 mmHg supine to 68/43 mmHg standing), but a concomitant fall in pulse suggests this was vaso-vagal in nature.

A30.6. Summary   Placebo-subtracted effects on supine and standing blood pressure averaged -8/-6 mmHg and -11/-9 mmHg, respectively. Little change in heart rate accompanied changes in blood pressure, but that may have been related to the background antihypertensive agent used. Blood pressure effects had onset within half an hour and persisted for several hours. Although substantial, subjects were not symptomatic, at least under the controlled clinical conditions.

Study 148-226: An open, randomised, single oral dose, three way crossover bioequivalence study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100mg as capsules and tablets in the

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A31. Study 148-226: An open, randomised, single oral dose, three way crossover bioequivalence study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100mg as capsules and tablets in the fasted state.

A31.1. Source documents	Study protocol NDA 20-895, vol 1.71; study report: NDA vol 1.71; electronic document: 47081254.pdf.
A31.2. Investigators	Dr. D. Kleinermans, Pfizer Clinical Research Unit, Hopital Erasme ,Route de Lennik 808, 1070 Bruxelles, Belgium.
A31.3. Study dates	12 June 1996 to 29 July 1996.
A31.4. Study design	This study description was based upon the final study report, dated 4 July 1997.
A31.4.1. Objectives	The objectives were

The objectives were
- To compare the pharmacokinetics of sildenafil and the metabolite UK-103,320 following single oral doses of research capsules (4x25 mg), research tablet (1x100 mg) and commercial tablet (1x100 mg) in the fasted state and determine bioequivalence between formulations.
- To assess the safety and toleration of single 100-mg doses of sildenafil in healthy male subjects.

A31.4.2. Formulation

Drug supplies were 25-mg capsules (lot 3509-051, size 35,000), 100-mg tablets (lot 4469-119, size 61,358) and the to-be-marketed 100-mg tablet formulation (lot N6060, size 216,721).

A31.4.3. Population

A total of 36 healthy male volunteers, age 18 to 45, were recruited.

A31.4.4. Procedures

This was an open, randomised, single-dose, three-way crossover bioequivalence study. After an overnight fast, dosing took place between 0700 and 0900 on each dosing day. There was a minimum of a 6-day washout period between treatments. Plasma samples were collected before each dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

A31.4.5. Assay

A31.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. C_{max} and AUC were log-transformed. The Schuirman two one-sided test was applied using a bioequivalence interval of 80 to 125%.

A31.4.7. Safety

Routine safety data were recorded.

A31.5. Results

A31.5.1. Conduct

Thirty-seven subjects were recruited and all but one completed all study phases. Protocol violations appear to have been minor.

A31.5.2. Pharmacokinetics

Mean plasma concentration time profiles for sildenafil and its metabolite for the three treatments are shown in Figure 56 below and the corresponding parameters along with the relevant 90% confidence intervals are summarized in Table 1.

Study 148-226: An open, randomised, single oral dose, three way crossover bioequivalence study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100mg as capsules and tablets in the

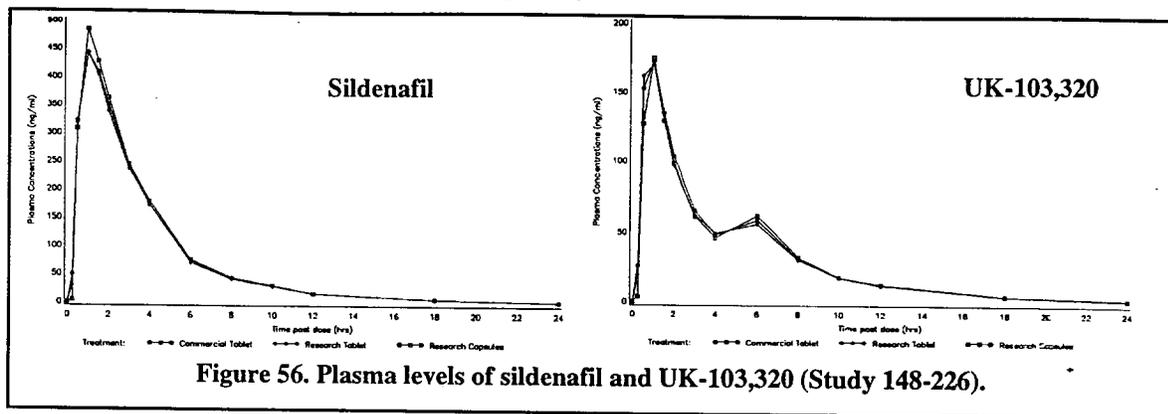*NDA 20-895*
Sildenafil for male impotence

Figure 56. Plasma levels of sildenafil and UK-103,320 (Study 148-226).

Table 120. Pharmacokinetic parameters (Study 148-226).

	Research formulation		Commercial	Ratios (90% CI)		
	25-mg capsule	100-mg tablet	100-mg tablet	Commercial: research tab	Commercial: research cap	Research tab: research cap
C_{max} (ng/mL)	478	446	438	0.99 (0.92-1.07)	0.97 (0.90-1.05)	0.98 (0.91-1.06)
T_{max} (h)	1.1	1.1	1.1	—	—	—
AUC (ng.h/mL)	1645	1540	1609	1.05 (0.99-1.11)	1.01 (0.96-1.07)	0.96 (0.91-1.02)
AUC_τ (ng.h/mL)	1629	1526	1593	—	—	—
k_{el} (h^{-1})	0.22	0.21	0.23	—	—	—
$t_{1/2}$ (h)	3.2	3.3	3.1	—	—	—

A31.5.3. Safety   There were no serious or severe adverse events reported. Headache, vasodilation, abnormal vision, and penile erections were reported with all treatments.

A31.6. Summary   The results of the study show that the research tablet, the commercial tablet and the research capsule are all bioequivalent to each other.

Study 148-227: An open randomised, single oral dose, two way crossover study to   *NDA 20-895*
determine the pharmacokinetics of sildenafil in healthy male volunteers following   *Sildenafil for male impotence*
administration of 100 mg as commercial tablets in the fed and fasted state.

A32. Study 148-227: An open randomised, single oral dose, two way crossover study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100 mg as commercial tablets in the fed and fasted state.

A32.1. Source documents	Study protocol NDA 20-895, vol 1.72; study report: NDA vol 1.72; electronic document: 46660186.pdf.
A32.2. Investigators	
A32.3. Study dates	3 June 1996 to 4 August 1996.
A32.4. Study design	This study description was based upon the final study report, dated 21 July 1997.

A32.4.1. Objectives

The objectives were
- To compare the pharmacokinetics of sildenafil and the metabolite (UK-103,320) following single oral doses of commercial tablets (1x100 mg) in the fed and fasted states.
- To assess the safety and toleration of sildenafil 100 mg in healthy male subjects.

A32.4.2. Formulation   Drug supplies were the to-be-marketed 100-mg tablet formulation, lot 6060.

A32.4.3. Population   A total of 34 healthy male volunteers, age 18 to 45, were recruited.

A32.4.4. Procedures

The study was an open, randomized, two-way crossover single-dose study of sildenafil commercial 100-mg tablets under fed and fasted states. There was a washout period of at least 7 days between treatments. After an overnight fast, subjects in the fed arm of the study received a high-fat breakfast consisting of: 2 fried eggs in vegetable oil, 2 bacon rashers grilled, 1 slice of white bread toasted with butter, 90 gm of hash brown potatoes, 240 ml full fat milk. A standard lunch and dinner were served after the 4-hour and 10-hour post-dosing blood samples.

During each treatment period, 7-ml blood samples were collected at the following times: 0, 0.25, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18 and 24-hours post-dose.

A32.4.5. Assay

A32.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Ninety percent confidence intervals were calculated on the ratios of the log-transformed C_{max} and AUC in the fasted and fed states.

A32.4.7. Safety   Routine safety data were recorded.

A32.5. Results

A32.5.1. Conduct

All 34 subjects completed both study phases. Protocol violations appear to have been minor.

A32.5.2. Pharmacokinetics

Mean plasma concentrations vs. time profiles for sildenafil and its metabolite in both the fed and fasted states are shown in Figure 57 below. The corresponding pharmacokinetic parameters are summarized in Table 121 below. The results of the study seem to indicate that food slowed the rate of absorption of sildenafil since C_{max} decreased by 29% and T_{max} was prolonged by 1 hour. The relative bioavailability fed/fasted was 89%.

Study 148-227: An open randomised, single oral dose, two way crossover study to determine the pharmacokinetics of sildenafil in healthy male volunteers following administration of 100 mg as commercial tablets in the fed and fasted state.

NDA 20-895
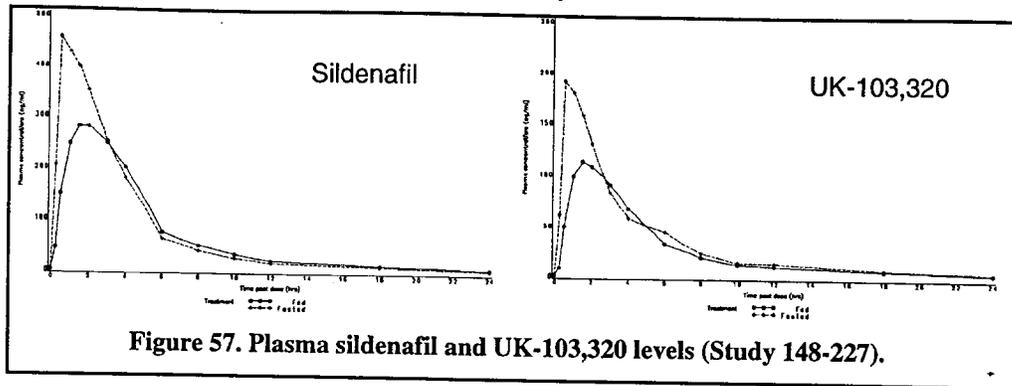*· Sildenafil for male impotence*

Figure 57. Plasma sildenafil and UK-103,320 levels (Study 148-227).

Table 121. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-227).

	Sildenafil		UK-103,320	
	Fed	Fasted	Fed	Fasted
C_{max} (ng/mL)	364	514	137	215
T_{max} (h)	2.0	1.0	1.9	0.9
AUC (ng.h/mL)	1489	1651	571	729
AUC_τ (ng.h/mL)	1465	1651	547	700
k_{el} (h-1)	0.16	0.17	0.11	0.12
$t_{1/2}$ (h)	4.3	4.0	6.1	5.9

A32.5.3. Safety

There were no serious or severe adverse events reported. Headache and visual defects were the most common adverse events. Penile erections were reported by 1 subject in the fasted state and 4 subjects in the fed state.

A32.6. Summary

The results of the study showed that coadministration of a high-fast breakfast with sildenafil slightly decreased its rate of absorption. However, this decrease in the rate of absorption is not expected to have any clinical consequences.

Study 148-228: An open, randomised, single oral dose, four way crossover study to   *NDA 20-895*
determine the dose proportionality of the pharmacokinetics of sildenafil in healthy   *Sildenafil for male impotence*
male volunteers over the dose range 25mg to 200mg.

A33. Study 148-228: An open, randomised, single oral dose, four way crossover study to determine the dose proportionality of the pharmacokinetics of sildenafil in healthy male volunteers over the dose range 25mg to 200mg.

A33.1. Source documents	Study protocol NDA 20-895, vol 1.73; study report: NDA vol 1.73; electronic document: 47111104.pdf.
A33.2. Investigators	
A33.3. Study dates	10 June 1996 to 10 September 1996.
A33.4. Study design	This study description was based upon the final study report, dated 8 August 1997.

A33.4.1. Objectives

The objectives were
* To determine the dose proportionality of the pharmacokinetics of sildenafil following single oral doses of the commercial tablet over the dose range 25 to 200 mg.
* To assess the safety and toleration of single doses (25 to 200 mg) of sildenafil in healthy male subjects.

A33.4.2. Formulation

Drug supplies were to the to-be-marketed tablet formulation shown in Table 122 below.

Table 122. Drug supplies (Study 148-228).

	Lot		Lot		Lot
25 mg tablet	N6056	50 mg tablet	N6058	100 mg tablet	N6060

A33.4.3. Population

A total of 32 health male volunteers, age 18 to 45, were to be recruited.

A33.4.4. Procedures

In random order and separated by 7 days, subjects received oral doses of sildenafil 1x25 mg, 1x50 mg, 1x100 mg, and 2x100 mg in the morning after overnight fast. Subjects continued to fast for 4 hours after dosing.

Blood samples for plasma levels of sildenafil and UK-103,320 were obtained pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

A33.4.5. Assay

A33.4.6. Analysis

The following pharmacokinetic parameters were calculated: C_{max}, T_{max}, AUC_τ, AUC, k_{el}, and $t_{1/2}$.

A33.4.7. Safety

Routine safety data were recorded.

A33.5. Results

A33.5.1. Conduct

Thirty-three subjects were randomized and treated. One was withdrawn after the first study period because of protocol violations. Other protocol violations appear to have been minor.

A33.5.2. Pharmacokinetics

Mean plasma levels of sildenafil and UK-103,320 are shown as a function of dose in Figure 58 below. Pharmacodynamic parameters are shown in Table 123 below.

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[1] However, the same assay was used in other trials for which adequate documentation was provided.

Study 148-228: An open, randomised, single oral dose, four way crossover study to determine the dose proportionality of the pharmacokinetics of sildenafil in healthy male volunteers over the dose range 25mg to 200mg.

NDA 20-895
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Table 123. Pharmacokinetic parameters for sildenafil and UK-103,320 (Study 148-228).

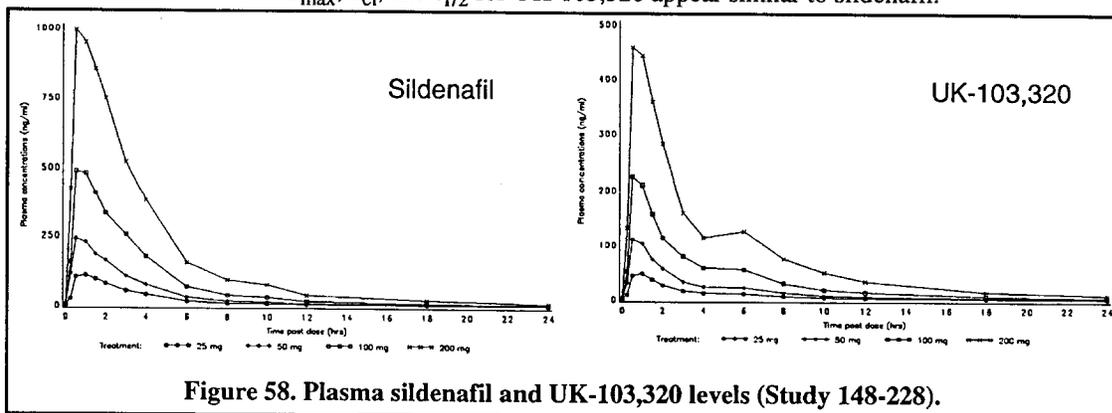|	Sildenafil				UK-103,320			
	25	50	100	200	25	50	100	200
C_{max} (ng/mL)	127	271	560	1150	54	126	254	526
T_{max} (h)	1.02	0.79	0.83	0.94	0.97	0.78	0.77	0.88
AUC (ng.h/mL)	361	738	1685	3755	147	328	776	1822
AUC_τ (ng.h/mL)	334	727	1667	3702	134	318	756	1772
k_{el} (h-1)	0.27	0.23	0.19	0.18	0.24	0.20	0.15	0.14
$t_{1/2}$ (h)	2.6	3.0	3.7	3.8	2.9	3.5	4.6	4.9

The sponsor's analyses of dose-normalized ratios of geometric means for AUC and C_{max} for sildenafil increase with the ratio of doses, as shown in Table 124 below. The AUC and C_{max} for sildenafil increase more than dose-proportionally; a doubling of dose increases AUC by 2.23 and C_{max} by 2.08.

Table 124. Test of dose-proportionality for AUC and C_{max} of sildenafil (Study 148-228).

	AUC		C_{max}	
	Ratio	90% CI	Ratio	90% CI
50/25	1.08	1.01-1.15	1.07	0.96-1.19
100/50	1.14	1.07-1.22	1.04	0.93-1.15
200/100	1.11	1.05-1.19	1.03	0.92-1.14
100/25	1.23	1.16-1.32	1.11	1.00-1.23
200/25	1.38	1.29-1.47	1.14	1.02-1.27

T_{max} for sildenafil did not appear to be a function of dose. The elimination rate constant, k_{el}, and $t_{1/2}$ were functions of dose.

Although not formally analyzed by the sponsor, the dose-relatedness of AUC, C_{max}, T_{max}, k_{el}, and $t_{1/2}$ for UK-103,320 appear similar to sildenafil.

Figure 58. Plasma sildenafil and UK-103,320 levels (Study 148-228).

A33.5.3. Safety

There were no serious or severe adverse events reported. Adverse events, total and treatment-related, increased with dose, with headache and visual defects being most common.

A33.6. Summary

When sildenafil is administered as single doses using the to-be-marketed tablet formulation, AUC and C_{max} for sildenafil and metabolite UK-103,320 increase more

Study 148-228: An open, randomised, single oral dose, four way crossover study to
determine the dose proportionality of the pharmacokinetics of sildenafil in healthy
male volunteers over the dose range 25mg to 200mg.

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than proportionally with dose over the range of sildenafil 25 to 200 mg. This was true even for the 100- to 200-mg doses, both of which utilized the 100-mg tablets, suggesting that this effect is related to the drug substance rather than the formulation. The increase in AUC and C_{max} were associated with increased $t_{1/2}$ and reduced k_{el}, suggestive of a saturable elimination process.