Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Appendix A14, page 126 through Appendix A22.6, page 149

A14. 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.

A14.1. Source documents

Study protocol NDA 20-895, vol 1.112; study report: NDA vol 1.112; electronic document: 47090249.pdf.

A14.2. Investigators

Multi-center study with 27 investigators in Canada.

A14.3. Study dates

16 July 1996 to 6 January 1997.

A14.4. Study design

This study description was based upon the amended protocol dated 21 March 1996. There were no amendments.

Drug supplies are shown in Table 98 below.

Table 98. Drug supplies (Study 148-106).

	Lot		Lot
Placebo 50 mg	N5274-G1	Sildenafil 50 mg	4469-142B-G1
Placebo 100 mg	N5275-G1	Sildenafil 100 mg	N5277-G1

The intent was to randomize 460 male subjects age >18, with erectile dysfunction[1] of >6 months' duration, and in a heterosexual relationship for >6 months. Subjects were excluded for (1) anatomical deformities such as severe penile fibrosis, (2) other sexual disorders such as hypoactive sexual desire, (3) elevated prolactin (3x ULN) or low free testosterone (20% below LLN), (4) major, uncontrolled psychiatric disorders, (5) history of alcohol or drug abuse, (6) history of major hematologic, renal, or hepatic disorder, (7) erectile dysfunction following spinal cord injury, (8) uncontrolled diabetes or diabetic retinopathy, (9) stroke or myocardial infarction within 6 months, (10) cardiac failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months, (11) blood pressure outside 90/50 to 170/100 mmHg, (12) active peptic ulcer disease or bleeding disorder, (13) any clinically significant baseline laboratory abnormality, (14) need for anticoagulants, nitrates, androgens, or trazodone, (15) need for aspirin or NSAIDs and a history of peptic ulcer disease, (16) unwillingness to cease use of vacuum devices, intracavernosal injection, or other therapy for erectile dysfunction, (17) other experimental drug use within 3 months, or (18) history of retinitis pigmentosa.

At the end of a 4-week treatment-free run-in period during which baseline sexual performance data were collected, subjects were randomized equally to placebo or sildenafil 50, 100, or 200 mg and followed for 12 weeks. Subjects were instructed to take study drug approximately one hour before planned sexual activity, not more than once per day. Alcohol use during this hour was discouraged. Prior to clinic visits at the end of weeks 2, 4, 8, and 12, subjects also took study drug. Subjects completed an event log noting time of study drug administration and subsequent sexual activity. Subjects completing study without an adverse event were eligible for participation in an open-label follow-on study.

The primary efficacy assessment was at week 12. At this visit, subjects completed a global assessment question, sexual function questionnaire (containing the primary efficacy questions), and a quality of life questionnaire. Optionally, partners filled out another questionnaire.

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1. 'the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance'

Plasma samples were drawn for determination of parent compound and metabolite UK-103,320 at weeks 2, 4, 8, and 12, a random, but targeted and recorded, time after the last dose.

The study was originally sized to achieve 90% power at α=0.05 to detect a 75% improvement in erections on study drug compared with placebo. Randomization was not stratified.

The primary end point was the answer, at 12 weeks, to two questions on the sexual function questionnaire:

> *[3] Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?*
>
> *[4] Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?*

Both questions had the same set of possible responses, either "did not attempt intercourse" or a 5-level semi-quantitative response. Analysis was to be by ANCOVA, based on table scores, where the "no attempt" response was lumped with the worst frequency category. Each question was to be analyzed separately with $p<0.05$ on both necessary for demonstrating efficacy. The model was to include terms for center, baseline, and "other covariates deemed to be appropriate". The primary test was a single-degree-of-freedom test for a linear trend by dose. Any interim analyses were not to affect the ongoing trial.

The primary analysis was described as ITT with last observation carried forward. However, the sponsor's description of the ITT population includes only subjects with at least one observation post-randomization.

Secondary end points were (1) response to the global assessment question (originally the primary end point):

> *Has the treatment you have been taking over the past 4 weeks improved your erections? [yes] [no]*

(2) the responses to other sexual function questions (there were 13 in addition to the primary efficacy questions), (3) proportion of successful attempts at intercourse, determined from the event log, (4) responses on the optional partner questionnaire, (5) responses on the quality of life assessment, and (6) time to discontinuation for lack of efficacy.

Pharmacokinetic data were to be analyzed by nonlinear mixed-effect modeling (NONMEM) utilizing a large selection of baseline attributes as covariates.

Safety assessments included (1) ECGs at screening and week 12,(2) laboratory tests (CBC, SMA20, urinalysis), (3) vital signs, and (4) physical examination. Clinical adverse events and their relationship to the study drug were recorded.

A14.5. Results

A14.5.1. Conduct

Five hundred and eighty-two subjects were screened, 497 were randomized, and 436 (88%) completed study.

Demographics of the 4 treatment groups are shown in Table 99 below. About half of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 9% had used non-drug treatments.

Protocol violations are described in Table 100 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 99. Demographics (Study 148-106).

		Placebo N=122	Sildenafil 50 mg N=127	Sildenafil 100 mg N=124	Sildenafil 200 mg N=124
Race (%)	White	95	95	91	86
	Black	4.1	1.7	4.0	4.8
	Other	4.9	0.8	5.2	7.2
Age	Mean	57	60	58	58
	Range	25-79	39-80	24-80	21-79
Etiology (%)	Organic	59	62	58	53
	Psychogenic	14	18	16	18
	Mixed	27	19	26	29
Duration (y)	Mean	5.2	5.5	5.6	5.2
	Range	0.5-26	0.5-34	0.5-37	0.5-23
Med hx (%)	Hypertension	27	22	30	21
	Diabetes	18	22	12	17
	Peripheral vascular disease	4.9	3.9	3.2	0.8
	Depression	7.4	5.5	4.9	4.8
	IHD	17	15	16	15

Table 100. Protocol violations (Study 148-106).

At randomization	n	On treatment	n
Prohibited meds	3	>1 dose/day	36
Baseline lab abn	21	Blind broken for AE	5
Peyronie's disease or anatomic defect	24		
Active medical condition	8		
Ethanol or drug abuse	20		
Confounding condition/treatment	28		
Poorly controlled hypertension	2		
Hypogonadism	1		
Total[a]	130	Total	41

a. Some subjects had more than one violation.

Discontinuation rates were 11 to 15% in the 4 treatment groups, but most of the withdrawals from placebo were for lack of efficacy and most of the withdrawals from the 200-mg group were for treatment-related adverse events.

A14.5.2. Effectiveness

All randomized subjects with a post-randomization assessment were included in the sponsor's ITT analyses. Responses to IIEF questions 3 and 4 were scored as 0 for no attempts[2], 1 for never or rarely successful, etc., up to 5 for always or almost always successful. The sponsor's analyses was LOCF, which tends to make placebo, which had a higher withdrawal rate, better than it otherwise would be. Results are summarized in Table 101 below.

Secondary end points from the other IIEF questions are described in Table 102 below (sponsor's analyses only). All treatment effects were highly statistically significant,

2. Although this is not strictly as specified for this protocol, it is reasonable and in accordance with other phase III protocols and analyses.

Table 101. ITT analyses of IIEF questions 3 and 4 (Study 148-106).

		Placebo N=122		Sildenafil 50 mg N=127		100 mg N=124		200 mg N=124		*P*
		n	Q	n	Q	n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	1.8[a]	—	—	—	—	—	—	
	Week 12	109	2.2	116	3.5	112	3.7	112	3.5	<0.0001
How often were you able to maintain your erection after penetration?	Baseline	—	1.5	—	—	—	—	—	—	
	Week 12	109	1.7	115	3.2	112	3.6	112	3.4	<0.0001

a. This is apparently the pooled baseline value for all subjects.

except for one pertaining to sexual desire, for which there appeared to be no treatment effect.

Table 102. ITT analyses of non-primary IIEF questions at week 12 (Study 148-106)[a].

Domain	Question	Base-line	Placebo N=216		Sildenafil 25 mg N=102		50 mg N=107		100 mg N=107		*P*
			n	Q	n	Q	n	Q	n	Q	
Erectile function	Able to get erection	2.3	108	2.3	116	3.3	112	3.7	112	3.7	<0.0001
	Erections hard enough	1.8	110	2.0	116	3.3	112	3.6	112	3.4	<0.0001
	Erection maintained to completion	1.5	110	1.7	116	3.4	113	3.6	112	3.4	<0.0001
	Confidence in erection	1.6	108	1.8	113	3.0	111	3.2	110	3.1	<0.0001
Intercourse satisfaction	Attempted intercourse	2.0	110	2.7	116	3.3	113	3.3	112	3.2	0.001
	Satisfaction of intercourse	1.6	110	1.9	116	3.2	112	3.5	112	3.6	<0.0001
	Enjoyment of intercourse	1.8	110	1.9	115	3.1	112	3.2	112	3.2	<0.0001
Orgasmic function	Frequency of ejaculation	2.7	108	2.9	116	3.6	110	3.7	111	3.6	0.0002
	Frequency of orgasm	2.7	109	2.9	116	3.6	113	3.7	112	3.5	0.0002
Sexual desire	Frequency of desire	3.3	109	3.3	115	3.5	112	3.5	111	3.5	0.4
	Rating of desire	3.1	110	3.1	116	3.3	112	3.3	111	3.4	0.008
Overall satisfaction	Satisfaction with sex life	1.9	109	2.1	116	3.2	112	3.4	111	3.5	<0.0001
	Satisfaction with relationship	2.5	108	2.6	116	3.6	111	3.8	110	3.8	<0.0001

a. Sponsor's analyses.

About 11% of partners responded on the partner questionnaire; no treatment effect was demonstrated.

The global assessment by subjects whether treatment improved their erections, the original primary end point, was answered in the affirmative at week 12 by 25% on placebo, 70% on 50 mg, 82% on 100 mg, and 80% on 200 mg.

The sponsor's analysis of the event logs focussed on the proportion of successful attempts at intercourse, but did not describe the number of such attempts by treatment group, or the success rate for subjects. The success rates were 15%, 45%, 49%, and 49% on placebo, 50 mg, 100 mg, and 200 mg.

The only quality of life component (out of 11) with a statistically significant treatment effect (by the sponsor's analyses), at week 12, was impact of erectile dysfunction on quality of life.

A14.5.3. Safety

Safety will be reviewed for all placebo-controlled experience together.

A14.6. Summary

SAS datasets were not made available for this study, so all analyses are the sponsor's. The study population appears to have been similar to that in other major studies. There were, as well, comparably robust and dose-related treatment effects, as assessed by erectile and sexual function questionnaires and by event log.

A15. Study 148-203: A single blind, four way crossover study to investigate the pharmacokinetics of and assess the safety and tolerance of UK-92480 after administration of escalating intravenous doses in the fasted state.

A15.1. Source documents

Study protocol NDA 20-895, vol 1.46; study report: NDA vol 1.46-1.47; electronic document: 47159495.pdf.

A15.2. Investigators

A15.3. Study dates

8 November 1991 to 31 December 1991.

A15.4. Study design

This study description was based upon the final study report, dated 16 October 1996.

A15.4.1. Objectives

The objectives were

- To assess the safety and toleration of intravenously administered sildenafil.
- To investigate the pharmacokinetics of sildenafil after IV administration.
- To assess the effect of sildenafil on plasma and/or platelet-rich plasma cGMP after IV administration.

A15.4.2. Formulation

Sildenafil was supplied as an injection solution 1 mg/ml (lot 975-19). Placebo was a 5% mannitol solution (lot 975-31).

A15.4.3. Population

Eight healthy male subjects between 45 and 60 years inclusive participated in this study.

A15.4.4. Procedures

The study was a single-blind four-way crossover dose escalation study of three single IV doses of sildenafil (20, 40, and 80 mg) plus a randomly inserted dose of placebo. Each dose was separated by a washout period of at least 7 days. The drug solutions was to be diluted with 5% mannitol solution. For each dose, 80 ml of solution was administered at 2 ml/min over 40 minutes. For the first study period, plasma samples were collected at 0, 20, 30, 40, and 50 minutes and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 32 and 48 hours post-dose. For the second, third and fourth study periods, additional samples were taken at 72 and 96 hours.

A15.4.5. Assay

A15.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. The linear relationship between log-dose and the log-transformed C_{max} or AUC was statistically evaluated. Pharmacokinetic parameters were deemed dose-proportional if the linear model was a good fit and the 95% confidence interval for the proportionality term included 1.

A15.4.7. Safety

Routine safety data were recorded.

A15.5. Results

A15.5.1. Pharmacokinetics

Mean plasma concentrations vs. time profiles for sildenafil and its main metabolite are shown as a function of dose in Figure 35 below with the corresponding pharmacokinetic parameters summarized in Table 103 below.

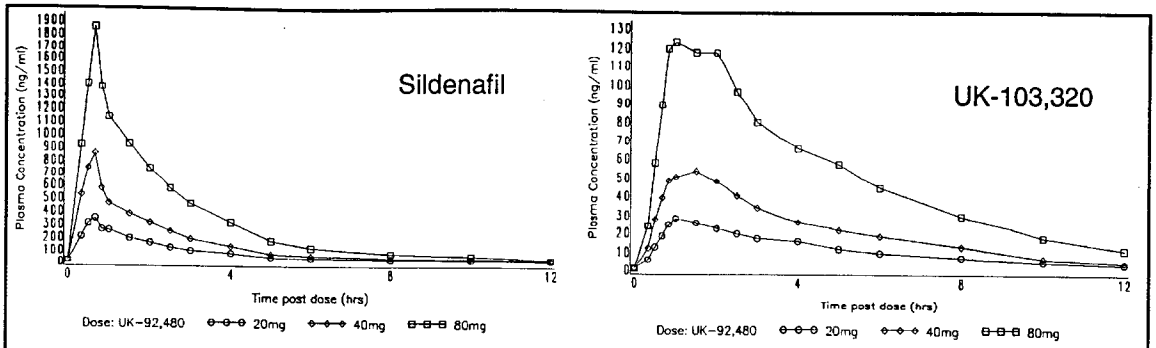

Figure 35. Plasma levels of sildenafil and UK-103,320 after IV dosing (Study 148-203).

Table 103. Pharmacokinetic parameters after IV dosing (Study 148-203).

	Sildenafil			UK-103,320		
	20 mg	40 mg	80 mg	20 mg	40 mg	80 mg
C_{max} (ng/ml)	331	833	1822	27	50	124
AUC_{τ} (ng.h/ml)	714	1554	3711	119	220	584
T_{max} (h)	0.67	0.58	0.69	1.17	1.17	1.33

The sponsor's analysis showed that both AUC and C_{max} for sildenafil, shown in Figure 36 below, were slightly more than dose proportional. The proportionality factor for C_{max} was 1.23 with a 95% CI of 1.1 to 1.36. For AUC the proportionality factor was 1.19 with a 95% CI of 1.09 to 1.29.

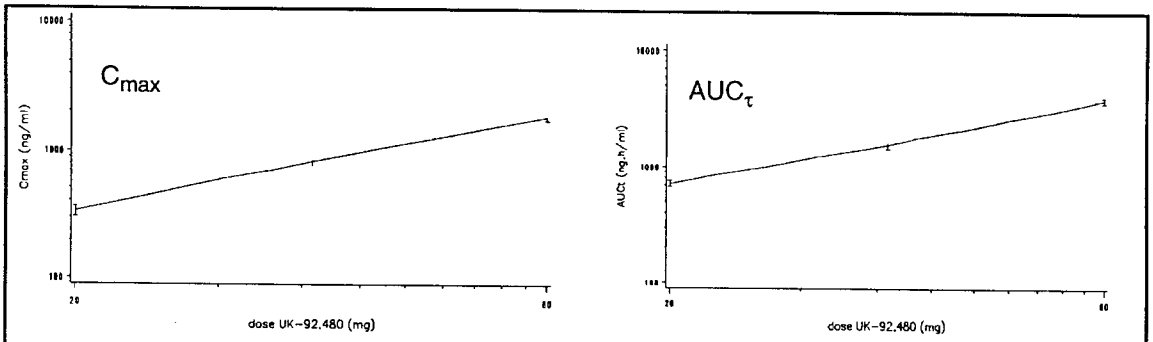

Figure 36. Log-log plots of C_{max} and AUC for sildenafil after IV dosing (Study 148-203).

For metabolite UK 103,320, both C_{max} and AUC increased in a dose-proportional manner. The proportionality factor for C_{max} was 1.09 with a 95% CI of 0.93-1.25 and for AUC it was 1.15 with a 95% CI of 0.96-1.34.

A15.6. Summary

The results of the study showed that after IV infusion of sildenafil 20 to 80 mg over 40 minutes, AUC and C_{max} for sildenafil exhibited a slight nonlinearity with dose. AUC and C_{max} for UK-103,320 appeared to be similar functions of dose, but wider confidence limits prevent one from excluding dose-proportionality for the metabolite.

A16. Study 148-204: An open study in normal volunteers to investigate the effects of an escalating brachial artery infusion of UK-92,480 on forearm blood flow and forearm venous compliance.

A16.1. Source documents

Study protocol NDA 20-895, vol 1.48; study report: NDA vol 1.48; electronic document: 47059260.pdf.

A16.2. Investigators

Single-center study with 1 investigator in the UK.

A16.3. Study dates

10 January 1992 to 23 April 1992.

A16.4. Study design

This study description was based upon the final study report, dated 26 March 1997.

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

Subjects received open-label 10-minute brachial artery infusions of dextrose 5%, dextrose 5%, mannitol 5%, sildenafil 0.3 to 100 µg/min (later changed to 3 to 300 µg/min), dextrose, and dextrose. All but the first dextrose infusions were accompanied by noradrenaline 0.5 to 2 µg/min. Some subjects returned for a second mannitol infusion on day 2. Forearm blood flow and venous compliance were measured during the latter half of each infusion, using standard techniques.

Routine safety data were recorded.

A16.5. Results

A16.5.1. Conduct

Thirteen subjects were recruited, but only 12 were dosed. All but 1 subject were Caucasian.

A16.5.2. Pharmacokinetics

Although plasma drug levels were recorded, they were not reported a fashion amenable to comparison with pharmacodynamic results.

A16.5.3. Pharmacodynamics

Forearm blood flow increased by 16% at 3 µg/min, and by 50% at 300 µg/min. Forearm volume increased by about 15% at the highest dose.

A16.5.4. Safety

No adverse events and no significant laboratory abnormalities were reported.

A16.6. Summary

Forearm vessel tone was set by noradrenaline infusion and antagonized by sildenafil in a dose-related manner.

A17. Study 148-206: A single blind, two way crossover, placebo controlled pilot study to investigate the effects of UK-92,480 (sildenafil) on platelet function in normal male volunteers.

A17.1. Source documents

Study protocol NDA 20-895, vol 1.50; study report: NDA vol 1.50; electronic document: 47164938.pdf.

A17.2. Investigators

Single-center study with 1 investigator in the UK.

A17.3. Study dates

24 March 1992 to 20 May 1992.

A17.4. Study design

This study description was based upon the final study report, dated 29 July 1997.

A total of 8 health male volunteers, age 18 to 45, were to be recruited.

This was a crossover study. During the two phases, subjects received 2 doses of either placebo or sildenafil 50 mg, 16 hours apart. The two phases were at least 10 days apart. After each dose, subjects had blood drawn at 2, 8, and 12 hours for measurement of sildenafil and metabolite and for assessment of platelet aggregability.

Platelet aggregation in plasma was assessed by a dose-response relationship for the IC_{50} for sodium nitroprusside inhibition of aggregation by ADP, with and without superoxide dismutase (to prolong the lifetime of nitric oxide). The aggregation of platelets in whole blood was assessed as the response to ADP.

Routine safety data were recorded.

A17.5. Results

A17.5.1. Conduct

Eight subjects were recruited and dosed.

A17.5.2. Pharmacokinetics

Although plasma drug levels were recorded, the study is too small to allow comparison with pharmacodynamic results.

A17.5.3. Pharmacodynamics

ADP produces platelet aggregation. Sodium nitroprusside antagonizes aggregation caused by ADP. Greater antagonism was observed in the presence of sildenafil. At about the time of the peak sildenafil concentration, the effect was about a 10-fold decrease in the IC_{50} for sodium nitroprusside. No effect on platelets was observed in whole blood.

Sildenafil had no effect on bleeding time.

A17.5.4. Safety

No serious adverse events or discontinuations and no significant laboratory abnormalities were reported.

A17.6. Summary

These results are consistent with sildenafil having no direct effect on platelet aggregation. However, in the presence of sodium nitroprusside, a donor of nitric oxide, platelet aggregation was enhanced.

A18. Study 148-207: A double blind, placebo controlled, single dose study followed by a double blind, placebo controlled 10-day multiple dose study to investigate the pharmacokinetics, platelet effects, safety and toleration of UK-92,480 (sildenafil) in healthy male volunteers.

A18.1. Source documents

Study protocol NDA 20-895, vol 1.51; study report: NDA vol 1.51; electronic document: 47053693.pdf.

A18.2. Investigators

A18.3. Study dates

25 February 1992 to 22 May 1992.

A18.4. Study design

This study description was based upon the final study report, dated 23 July 1997.

A18.4.1. Objectives

The objectives were

- To assess the pharmacokinetics of sildenafil following single and multiple capsule doses.
- To assess the safety and toleration of multiple doses of sildenafil.
- To assess the effects of single and multiple doses of sildenafil on platelet aggregability

A18.4.2. Formulation

Drug supplies were 25-mg capsules, lot 979-12 and matching placebo capsules, lot 748-43.

A18.4.3. Population

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

A18.4.4. Procedures

Subjects were equally randomized to placebo or sildenafil 25, 50, or 75 mg and received a single morning dose of study drug after overnight fast. At least 14 days later, they began thrice-daily dosing for 8 days and a single morning dose on day 9. Pharmacokinetic data were collected during the single-dose phase (0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 32, 48, 72, and 96 hours after dosing) and on days 0, 4, (0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing) and 9 (sampling as in single-dose phase) of the multiple-dose phase.

Platelet aggregation in plasma was assessed by a dose-response relationship for the IC_{50} for sodium nitroprusside inhibition of aggregation by ADP.

A18.4.5. Assay

A18.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. The predicted accumulation was calculated as AUC_{SD} / $AUC_{0\text{-}8h,SD}$. The observed accumulation was calculated as $AUC_{0\text{-}8h}$ (day 4 or day 9) / $AUC_{0\text{-}8h,SD}$. A repeated measure analysis of variance model was fitted to each pharmacokinetic parameter in turn, allowing for the effects of dose, subject within dose, day, and dose

by day interaction. Each of the following effects were tested: dose against subject within dose, and day and dose by day interaction against the residual. Each comparison of the pharmacokinetic parameters of interest was made using a two-sample t-test with the estimate of variability taken from the ANOVA. For the comparisons of $AUC_{0\text{-}8h}$, AUC, and C_{max}, the mean difference and 90% confidence limits of the mean difference were shown on a log-scale together with the transformed mean difference ratio (ratio of geometric means expressed as a percentage) and back-transformed 90% confidence limits of the ratio.

A18.4.7. Safety

Routine safety data were recorded. In addition, visual impairment was assessed with tests for visual acuity, color perception, and pupil response to light.

A18.5. Results

A18.5.1. Conduct

Thirty-eight subjects were recruited and dosed (9 to 10 per treatment group).

A18.5.2. Pharmacokinetics

Mean plasma concentration time profiles for sildenafil for both the single and multiple dose periods for the 25-, 50-, and 75-mg doses are shown in Figure 37 below. The corresponding pharmacokinetic parameters are summarized in Table 104 below. Figure 38 below shows the relationship between $AUC_{0\text{-}8h}$ and C_{max} for sildenafil and the sildenafil dose. Figure 39 below shows the mean plasma concentration profiles for metabolite UK-103,320 for the single and multiple dose periods at a dose of 75 mg.

The results of the study suggest some nonlinearity in C_{max} and AUC appearing by the 75-mg dose level. Thrice-daily administration of sildenafil produced slight accumulation at all of the studied doses. The accumulation ratios between day 9 and single dose administration, based on $AUC_{0\text{-}8h}$, for the 25-, 50-,

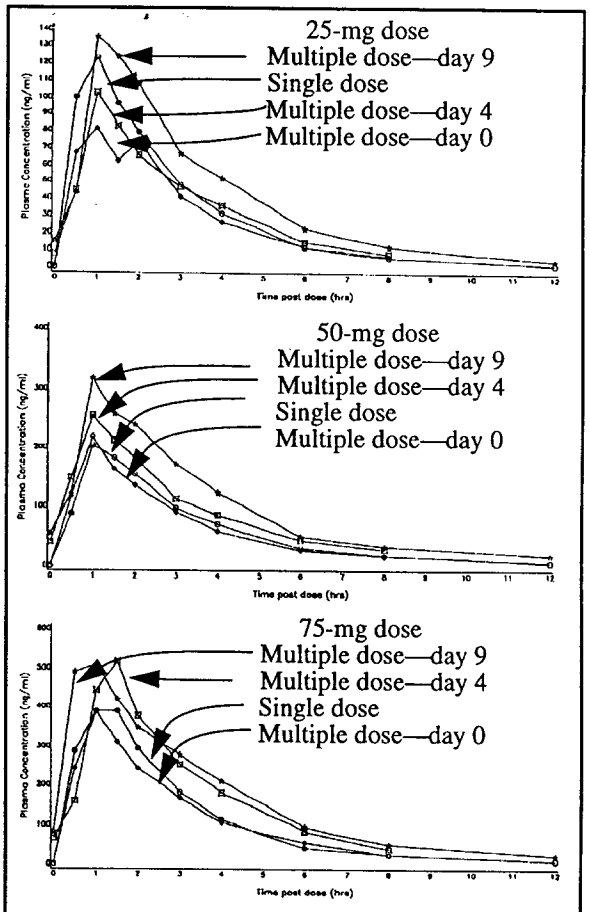

Figure 37. Plasma sildenafil levels after single and multiple dosing (Study 148-207).

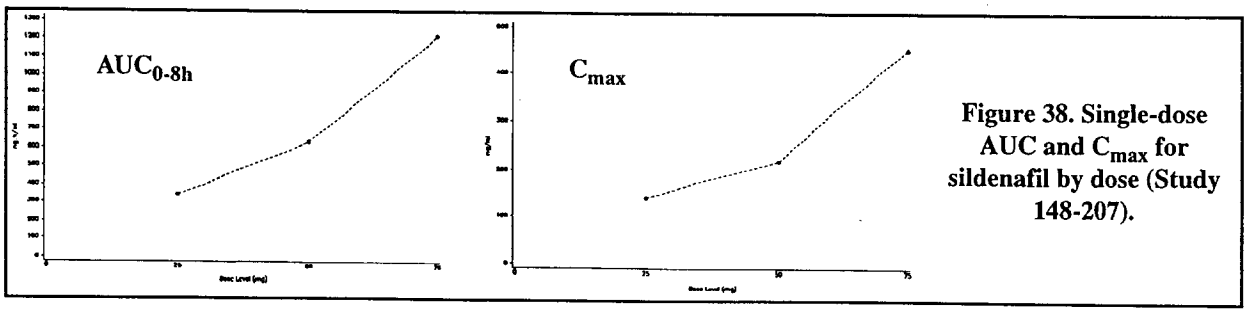

Figure 38. Single-dose AUC and C_{max} for sildenafil by dose (Study 148-207).

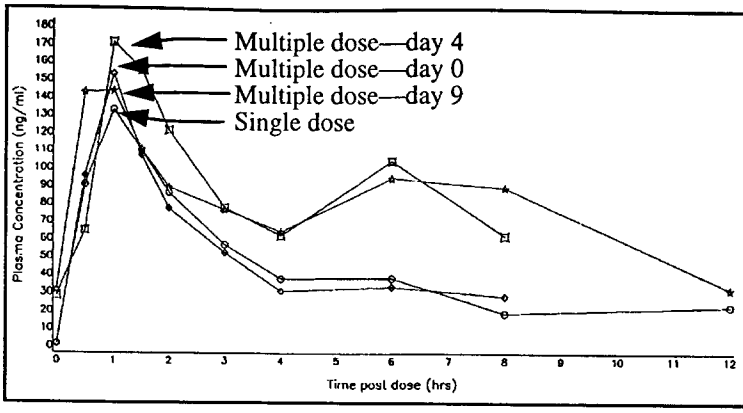

Figure 39. Plasma levels of UK-103,320 after single and multiple doses of sildenafil 75 mg (Study 148-207).

Table 104. Pharmacokinetic parameters after single and multiple dosing (Study 148-207).

	Day	Sildenafil dose				Day	Sildenafil dose		
		25 mg	50 mg	75 mg			25 mg	50 mg	75 mg
C_{max} (ng/mL)	SD	133	200	437	AUC_{0-8h} (ng.h/mL)	SD	320	583	1168
	MD0	99	211	421		MD0	254	575	1060
	MD4	104	229	519		MD4	292	701	1517
	MD9	141	310	494		MD9	403	929	1707
T_{max} (h)	SD	0.95	1.22	1.11	k_{el} (h^{-1})	SD	0.17	0.14	—
	MD0	1.05	0.94	1.06		MD0	—	—	—
	MD4	1.44	1.17	1.36		MD4	—	—	—
	MD9	1.28	1.39	1.25		MD9	0.16	0.15	—
AUC (ng.h/mL)	SD	346	662	1212	$t_{1/2}$ (h)	SD	4.0	4.8	—
	MD0	—				MD0	—	—	—
	MD4	—				MD4	—	—	—
	MD9	461	1107	1950		MD9	4.4	4.8	—

and 75-mg doses were 1.26, 1.59, and 1.32 respectively. The accumulation ratios, based on C_{max}, were 1.07, 1.55, and 1.09, respectively.

Plasma concentrations of the metabolite UK-103,320 were analyzed for the 75-mg dose. The results of this study show that its pharmacokinetics follow those of the parent drug, with about the same degree of accumulation with multiple dosing.

No attempt was made to compare plasma drug levels with pharmacodynamic results.

A18.5.3. Pharmacodynamics

ADP produces platelet aggregation. Sodium nitroprusside antagonizes aggregation caused by ADP. Measurements of the mean IC_{50} for sodium nitroprusside varied over 5-fold at various time points in the placebo group. Various measurements in the active treatment groups varied over essentially the same range, so that, although there appeared to be no treatment effect, there are quite wide confidence limits about this conclusion.

A18.5.4. Safety

No serious adverse events were reported. Apparently treatment-related adverse events included back pain, myalgia, headache, and penile erection. No visual disturbance adverse events were reported.

No subject showed a reduction in visual acuity. No statistically significant effect was found in pupillary response or color discrimination.

A18.6. Summary

Thrice-daily dosing from 25 to 75 mg resulted in a small degree of accumulation of sildenafil and metabolite UK-103,320. The AUC and C_{max} for sildenafil showed a slightly greater than linear dependence on dose. Sildenafil had no detectable effect on

platelet aggregation, although the trial could easily have missed a clinically significant effect. No effects of sildenafil were found on assessments of visual acuity, color discrimation, or pupillary response to light, at doses up to 75 mg/day.

A19. Study 148-208: An open randomised, two way crossover study to investigate the pharmacokinetics of UK-92480 after oral administration and IV administration in the fasted state.

A19.1. Source documents

Study protocol NDA 20-895, vol 1.53; study report: NDA vol 1.53; electronic document: 47154232.pdf.

A19.2. Investigators

A19.3. Study dates

7 September 1992 to 27 October 1992.

A19.4. Study design

This study description was based upon the final study report, dated 16 October 1996.

A19.4.1. Objectives

The objectives were

- To investigate the pharmacokinetics of sildenafil administered orally and intravenously and to determine its absolute oral bioavailability.
- To assess the safety and toleration of sildenafil 50 mg administered orally and intravenously.

A19.4.2. Formulation

Sildenafil 1 mg/ml injection solution was lot 975-30. Sildenafil 25 mg capsules were lot 979-12.

A19.4.3. Population

Twelve healthy male subjects between the ages 18 and 45 years participated in this study.

A19.4.4. Procedures

The study was an open, randomized, two-way crossover of two single doses of sildenafil 50 mg (oral and IV). On 2 study days separated by at least 10 days, subjects received, in random order, sildenafil 2x25 mg capsules or a 50 ml of 1 mg/ml solution infused at 1 ml/minute. After the IV dose of the drug, plasma samples were collected pre-dose and at 20, 30, 40, 50, 60, 75, and 90 minutes and at 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 32, 48, 72, 96 and 120 hours post dose. After the oral dose plasma samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 32, 48, 72, 96 and 120 hours post-dose.

A19.4.5. Assay

A19.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques.

A19.4.7. Safety

Routine safety data were recorded.

A19.5. Results

A19.5.1. Pharmacokinetics

Mean plasma concetrations time profile for sildenafil for both routes of administration are shown in Figure 40 below with the corresponding parameters summarized in Table 105 below.

Table 105. Pharmacokinetic parameters for sildenafil after IV and oral administration (Study 148-208).

	IV	PO		IV	PO
AUC (ng.h/mL)	1291	530	$t_{1/2}$ (h)	3.9	4.1
AUC_τ (ng.h/mL)	1289	528	CL (L/h)	41	—
C_{max} (ng/mL)	531	160	V (L)	234	—
T_{max} (h)	0.7	1.5	V_{ss} (L)	105	—
K_{el} (h^{-1})	0.18	0.17			

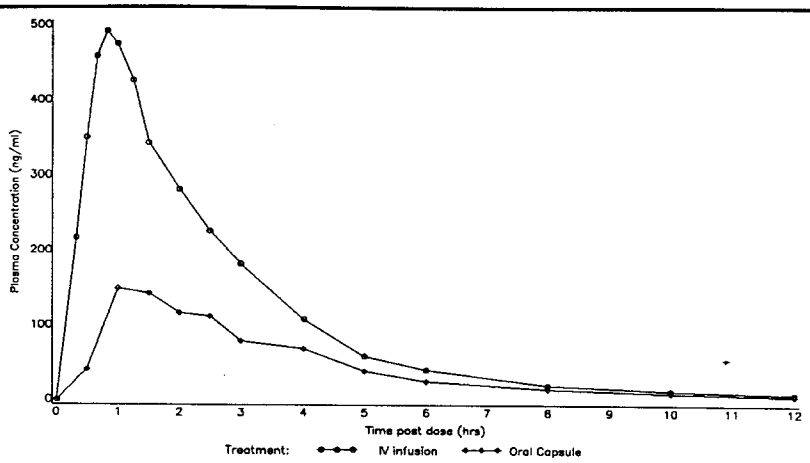

Figure 40. Mean plasma sildenafil after IV and oral dosing (Study 148-208).

The results of the study also seem to indicate that both V_{ss} and clearance are correlated to body weight as can be seen in Figure 41 below.

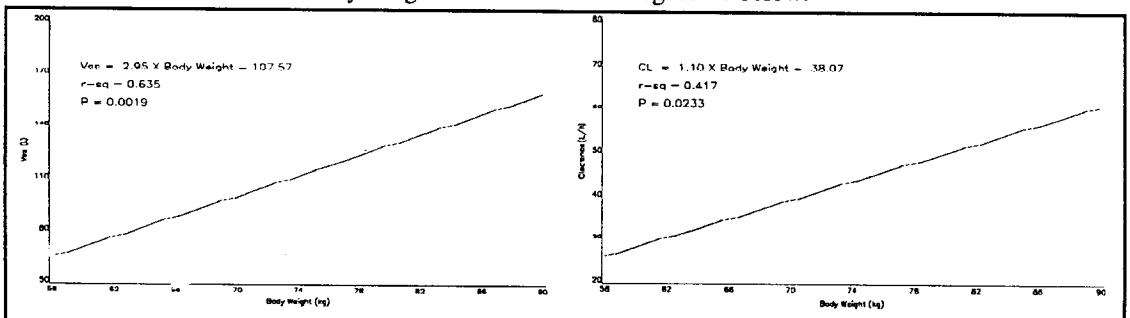

Figure 41. V_{ss} and clearance by body weight (Study 148-208).

Intravenous administration showed less inter-subject variability in K_{el} (10% CV) compared to the oral administration (21% CV).

A19.6. Summary

The results of the study showed that after a 50-mg dose, the absolute bioavailability of sildenafil was estimated to be 41%. The results are in good agreement with the ^{14}C study[1] in which the absolute bioavailability was estimated to be 38%.

1. *Study 148-215: An open, parallel group study to investigate the absorption, metabolism and excretion of a single oral and a single intravenous dose of radiolabeled [14C]-UK-92,480.* on page 145.

A20. Study 148-209: A double blind, randomised, placebo controlled, two-way crossover study to examine the effects of 25mg tid UK-92,480, administered as capsules, on the haemodynamic responses to glyceryl trinitrate in normal volunteers.

A20.1. Source documents

Study protocol NDA 20-895, vol 1.54; study report: NDA vol 1.54; electronic document: 47053170.pdf.

A20.2. Investigators

Single-center study with 1 investigator in the UK.

A20.3. Study dates

8 July 1992 to 13 September 1992.

A20.4. Study design

This study description was based upon the final study report, dated 19 March 1997.

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

In a crossover design, subjects received, in random order and separated by at least 10 days, placebo or sildenafil 25 mg tid for 4 days. On day 4, subjects received an intravenous infusion of glyceryl trinitrate stepped from 2.5 to 40 mg/min over 25 minutes while tilted at 70° (head up), and had vital signs monitored. The infusion was stopped when a subject's systolic pressure fell by 25 mmHg. This was repeated with a sublingual dose of 500 µg on day 5. Subjects spit out the tablet when they experienced symptomatic hypotension or systolic pressure fell 25 mmHg.

Blood samples were drawn for study drug levels once at the time of hemodynamic assessment.

Routine safety data were recorded.

A20.5. Results

A20.5.1. Conduct

Twelve subjects were randomized and completed both study phases. Four subjects did not have hemodynamic data returned for at least one session because of technical problems.

A20.5.2. Pharmacokinetics

At the time of hemodynamic assessment on days 4 and 5, mean plasma levels of sildenafil were about 160 ng/mL.

A20.5.3. Pharmacodynamics

Two of 12 subjects completed glyceryl trinitrate infusion on placebo, while none did so on sildenafil. The median time of infusion was 9 minutes on sildenafil vs. 13 minutes on placebo.

Similarly, with sublingual nitroglycerin, the median time was 4.5 minutes on sildenafil, but only 4 subjects on placebo stopped early. Blood pressure was reduced to a greater extent on sildenafil than on placebo (difference from baseline and placebo of about -15/-5 mmHg). Heart rate changes were not different on placebo and sildenafil.

A20.5.4. Safety

Adverse events other than hypotension with apparent relationship to study drug included headache, back pain, and myalgia. There were no serious or severe adverse events or laboratory abnormalities.

A20.6. Summary

Sildenafil augmented the hypotensive effect of glyceryl trinitrate, but had no discerible effect on blood pressure alone.

A21. Study 148-214: An open, parallel group study to determine the effects of impaired renal function on the pharmacokinetics, safety and toleration of sildenafil administered as a single 50 mg capsule dose.

A21.1. Source documents

Study protocol NDA 20-895, vol 1.59; study report: NDA vol 1.59; electronic document: 47053558.pdf.

A21.2. Investigators

A21.3. Study dates

7 November 1994 to 25 February 1995.

A21.4. Study design

This study description was based upon the final study report, dated 12 May 1997.

A21.4.1. Objectives

The objectives were

- To assess the plasma pharmacokinetics of sildenafil and the metabolite UK-103,320 after oral administration of a 50-mg capsule in the fasted state to subjects with varying degrees of renal function.
- To assess the safety and toleration of a single 50-mg dose of sildenafil in subjects with varying degrees of renal function.

A21.4.2. Formulation

Sildenafil 50-mg capsules were from lot 979-12.

A21.4.3. Population

A total of 24 male subjects between 18 and 70 years inclusive were to recruited into 4 treatment groups on the basis of baseline renal function: (a) healthy subjects with normal renal function (Cl_{cr} >80 mL/min), (b) subjects with mild renal impairment (Cl_{cr} between 50 and 80 mL/min), (c) subjects with moderate renal impairment (Cl_{cr} between 30 and 49 mL/min), and (d) subjects with severe renal impairment (Cl_{cr} <30 mL/min).

A21.4.4. Procedures

Subjects attended the clinical unit on the evening before dosing. On the morning of dosing (day 1), blood samples were collected immediately prior to dosing and at 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours post-dosing. An additional blood sample was collected immediately before dosing for protein binding determination and urine was collected from 0 to 24 hours post-dosing for the determination of creatinine clearance.

A21.4.5. Assay

A21.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Oral clearance for sildenafil was analyzed using regression techniques to investigate its relationship with creatinine clearance and age. In the first analysis, creatinine clearance was fitted first to examine whether it alone accounted for a significant amount of variability in Cl/f. Age was then fitted to determine whether it significantly explained significantly more of the variability. In the second analysis, age was fitted first followed by creatinine clearance. The choice of final model was based on the significance levels found in the previous two analyses. The same types of analyses were also done for AUC and C_{max}.

A21.4.7. Safety

Routine safety data were recorded.

A21.5. Results

A21.5.1. Pharmacokinetics

Mean plasma concentration vs. time profiles for sildenafil and its metabolite for the 4 groups of subjects with varying degrees of renal impairment are shown in Figure 42 below while the corresponding parameters are shown in Table 106 below. Figure 43 below shows the relationship between oral clearance of sildenafil and creatinine

clearance and between C_{max} for sildenafil and creatinine clearance. Figure 44 below shows the relationships between the oral clearance and age and between C_{max} and age.

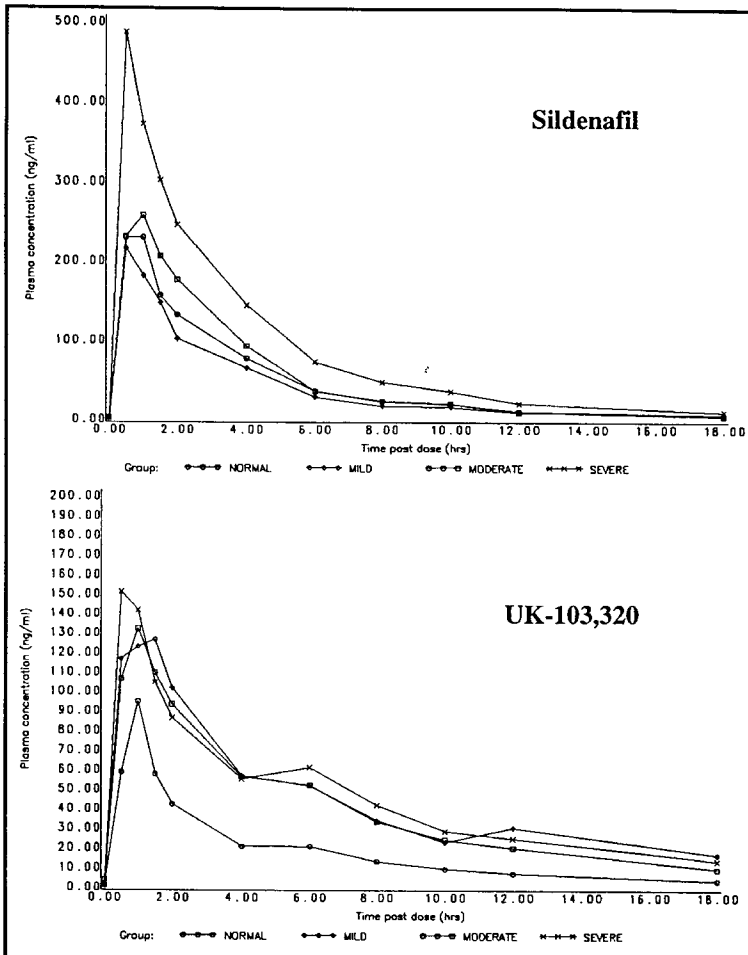

Figure 42. Plasma levels of sildenafil and UK-103,320 by time after dosing and degree of renal impairment (Study 148-214).

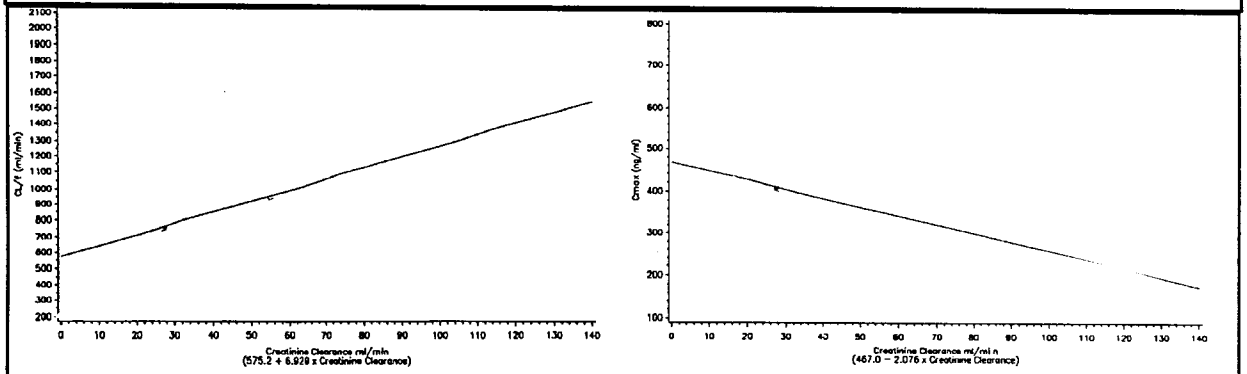

Figure 43. Clearance and C_{max} for sildenafil as a function of creatinine clearance (Study 148-214).

C_{max} in the severely impaired subjects was almost twice that in the normal group; the ratio of the geometric means was 1.88 with a 95% confidence interval of 1.24 to 2.87. The same trend was observed with AUC; severely impaired subjects had AUCs about twice as high as the group with normal renal function. Regression analysis of the C_{max} data revealed that creatinine clearance explained a significant amount (26%) of the variability (p=0.014) while age alone did not (p=0.191). Inclusion of age as an additional parameter in the regression model did not account for a significant amount of the variability above what was explained by creatinine clearance. Thus the model that best fits the C_{max} data is $C_{max} = 467 - 2.08 \times Cl_{cr}$.

Table 106. Pharmacokinetic parameters (Study 148-214).

	Cl_{cr} (mL/min)							
	Sildenafil				UK-103,320			
	>80 N=8	50-80 N=5	30-49 N=4	<30 N=7	>80 N=8	50-80 N=5	30-49 N=4	<30 N=7
Clearance/f (mL/min)	1102	1220	945	549	—	—	—	—
AUC (ng.h/mL)	756	683	882	1519	302	684	525	907
C_{max} (ng/mL)	246	256	288	464	87	151	103	156
T_{max} (h)	0.8	0.8	1.0	0.5	1.0	0.9	1.1	0.8
k_{el} (h^{-1})	0.20	0.16	0.23	0.18	0.13	0.09	0.12	0.09
$t_{1/2}$ (h)	3.4	4.2	3.0	3.9	5.4	7.7	5.9	7.7
PPB (% free)	2.7	2.4	2.0	2.2	3.4	2.9	2.5	2.6

Regression analyses of the oral clearance data revealed that creatinine clearance explained a significant amount of the variability (32%; p=0.05) while age alone did not (p=0.115). Thus, the best model to describe the relationship between oral clearance and creatinine clearance is $Cl/f = 575 + 6.93 \times Cl_{cr}$.

Analysis of the protein binding data revealed no significant difference between the groups in free fraction with mean values of 2.7, 2.4, 2 and 2.2% for the normal, mild, moderate, and severe groups respectively.

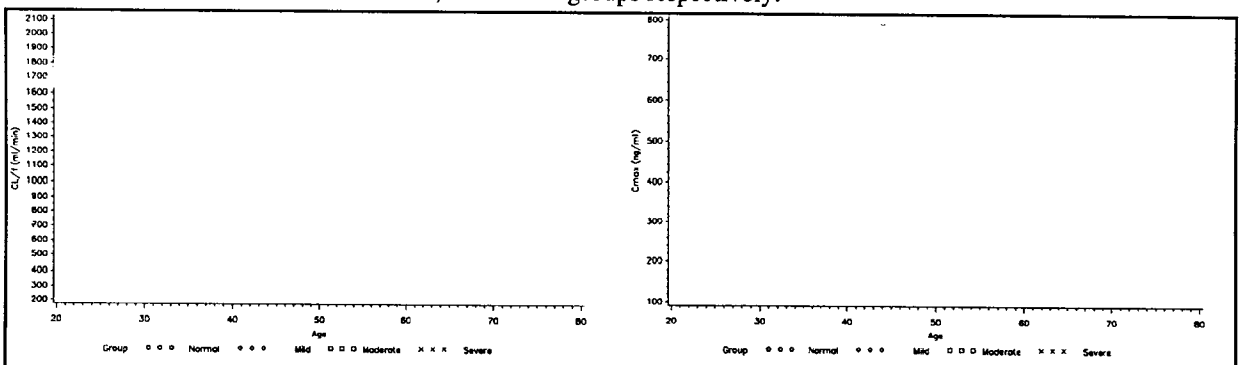

Figure 44. Clearance and C_{max} for sildenafil as a function of age (Study 148-214).

A21.5.2. Safety

There were no treatment-emergent adverse events reported.

A21.6. Summary

The results of the study showed that in patients the plasma levels of sildenafil and its metabolite UK-103,320 were almost doubled in subjects with severe renal impairment (creatinine clearance <30 mL/min) compared to subjects with normal renal function. This doubling of plasma concentrations might warrant the starting of certain subjects on lower dose of sildenafil—25 mg instead of 50 mg.

A22. Study 148-215: An open, parallel group study to investigate the absorption, metabolism and excretion of a single oral and a single intravenous dose of radiolabeled [^{14}C]-UK-92,480.

A22.1. Source documents

Study protocol NDA 20-895, vol 1.60; study report: NDA vol 1.60; electronic document: 47081663.pdf.

A22.2. Investigators

A22.3. Study dates

8 April 1995 to 8 May 1995.

A22.4. Study design

This study description was based upon the final study report, dated 6 August 1997.

A22.4.1. Objectives

The objectives were

- To measure the cumulative amount of drug related, radiolabeled material excreted in the urine and faces following a single dose of either oral (50mg) or IV (25 mg) [^{14}C]-sildenafil (nominally 50 μCi each).
- To characterize urinary and fecal radioactivity as unchanged sildenafil or its metabolites and, where possible, identify metabolites.
- To quantify blood and plasma total radioactivity and unchanged drug concentrations and, where possible, the major circulating metabolites following both oral and IV administration.

A22.4.2. Formulation

Sildenafil was to be supplied as powder for oral solution with sachets of sterile water (lot #3043-108) for reconstitution and as a 1 mg/ml solution for IV infusion (lot #3043-107). Each dose was to contain 50 μCi of radioactivity.

A22.4.3. Population

Six healthy male subjects between 45 and 60 years inclusive participated in this study.

A22.4.4. Procedures

The trial was an open, parallel group study of single oral and IV doses of ^{14}C-sildenafil. The oral dose was 50 mg and the IV dose was 25 mg, chosen to provide similar plasma concentrations. Three subjects received the oral solution and three subjects received the IV infusion. Subjects were to take 100 ml of oral solution. The bottle containing the oral solution was to be rinsed with 140 ml of potable water which was to be taken also. The 1-mg/ml IV infusion was to be given at 1 ml/min over 25 minutes.

After oral dosing, blood samples were collected at the following times: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 and 72 hours post-dose. After IV infusion, samples were taken at 5, 10, and 25 minutes and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, and 72 hours after the start of the infusion. Subsequent samples were to be taken at 24-hour intervals until the subject left the unit.

A urine sample was collected prior to dosing. After dosing all urine samples were collected for approximately 5 days post dose. The collection periods were as follows: 0-4, 4-8, 8-12, 12-24, 24-36, 36-48, 48-72, and 72-96 hours post-dose and subsequently at 24-hour intervals until less than 3 times baseline radioactivity level was reached.

All feces were collected into pre-weighed plastic containers in the 24 hours prior to dosing and at 24-hour intervals after dosing until approximately 5 days after dosing or until less than 3 times baseline radioactivity level was reached.

A22.4.5. Assay

A22.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. Oral absorption was estimated from the recovery ratios using the following formula:

$$\frac{\text{mean(urinary recovery/urinary+fecal recovery)}_{oral}}{\text{mean(urinary recovery/urinary+fecal recovery)}_{IV}}$$

A22.4.7. Safety

Routine safety data were recorded.

A22.5. Results

A22.5.1. Pharmacokinetics

Total radioactivity-time profiles in plasma and whole blood are shown in Figure 45 below for both routes of administration while the corresponding parameters are shown in Table 107 below.

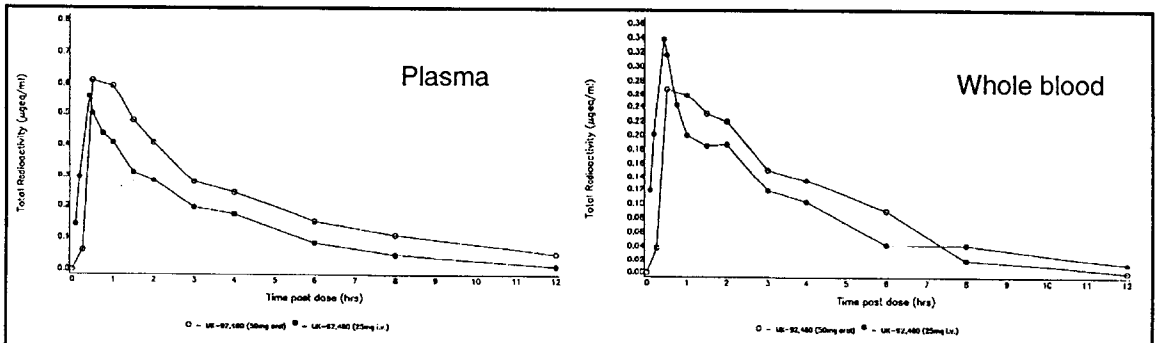

Figure 45. Plasma and whole-blood levels of total radioactivity after IV and oral dosing (Study 148-

Table 107. Pharmacokinetic parameters for total radioactivity after IV and oral dosing (Study 148-215).

	Sildenafil 25 mg IV		Sildenafil 50 mg oral	
	Plasma	Blood	Plasma	Blood
C_{max} (ng-eq/mL)	560	342	610	288
T_{max} (h)	0.53	0.45	1.1	0.97
AUC_T (ng-eq.h/mL)	1603	1012	2258	960

Values are means and ranges. The sponsor notes that estimates of C_{max} and T_{max} will have been affected by mis-sampling at early time points in orally-dosed subjects.

After IV administration the ratio of total radioactivity in plasma to whole blood based on geometric mean C_{max} and AUC was 1.64 and 1.58. The ratios after oral administration were 2.12 and 2.35, respectively. The difference between IV and oral administration was attributed to the presence of higher levels of metabolites which are more polar and have less tendency to partition into the red cells.

Mean plasma concentration profiles for sildenafil after IV and oral administration are shown in Figure 46 below with the corresponding pharmacokinetic parameters summarized in Table 108 below. The absolute bioavailability of sildenafil based on the ratio of AUC after oral and IV administration was calculated to be 38%.

Figure 47 below show the plasma concentration profiles for both UK-103,320 and UK-150,564, two of the main sildenafil metabolites, with the corresponding parameters summarized in Table 109 below.

The total amount of radioactivity recovered after IV infusion was 88.5% with 75.5% of radioactivity in the feces and 13.1% in the urine. Similar recoveries were observed after oral administration (91.3% of the dose with 79% in feces and 12.3% in urine).

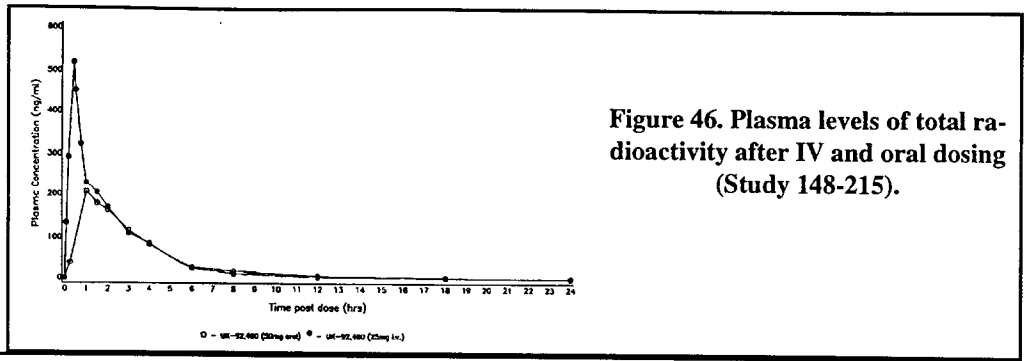

Figure 46. Plasma levels of total radioactivity after IV and oral dosing (Study 148-215).

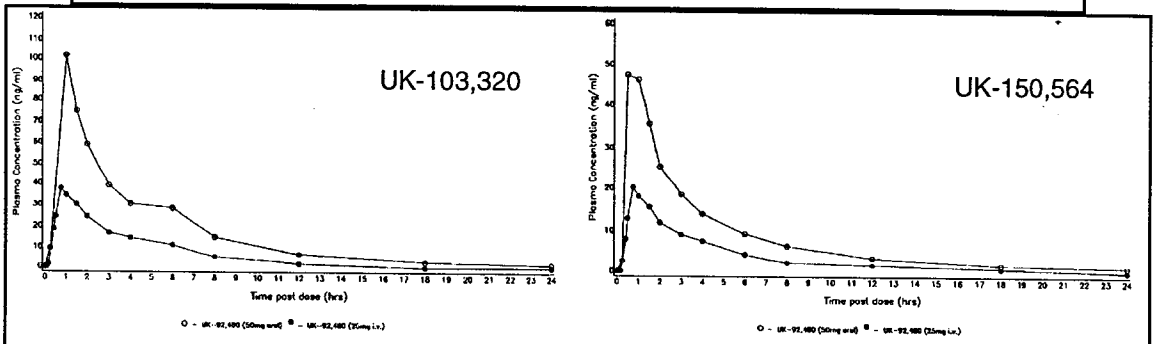

Figure 47. Plasma levels of sildenafil metabolites after IV and oral dosing (Study 148-215).

Table 108. Pharmacokinetic parameters for plasma sildenafil after IV and oral dosing (Study 148-215).

	25 mg IV	50 mg oral		25 mg IV	50 mg oral
C_{max} (ng/mL)	518	207	$t_{1/2}$ (h)	2.2	3.2
T_{max} (h)	0.42	1.17	CL_p (L/h)	26	—
AUC_τ (ng.h/mL)	964	721	V_d (L)	88	—
AUC (ng.h/mL)	971	729	V_{ss} (L)	57	—
k_{el} (h^{-1})	0.32	0.22			

Values are means and ranges. The sponsor notes that estimates of C_{max} and T_{max} will have been affected by mis-sampling at early time points in orally-dosed subjects.

Table 109. Pharmacokinetic parameters for sildenafil metabolites after IV and oral dosing (Study 148-215).

	UK-103,320		UK-150,564	
	25 mg IV	50 mg oral	25 mg IV	50 mg oral
C_{max} (ng-eq/mL)	38	101	19	49
T_{max} (h)	0.83	1.0	0.83	0.98
AUC_τ (ng-eq.h/mL)	139	389	76	179
AUC (ng.h/mL)	147	400	86	197
k_{el} (h^{-1})	0.30	0.13	0.13	0.10
$t_{1/2}$ (h)	2.3	5.5	5.4	7.0

Values are means and ranges. The sponsor notes that estimates of C_{max} and T_{max} will have been affected by mis-sampling at early time points in orally-dosed subjects.

Oral absorption as estimated from the above formula was 92%. Therefore, the low absolute bioavailability (38%) was due to first-pass metabolism and not due to incomplete absorption.

Sixty-eight percent of the plasma radioactivity after IV administration was accounted for by sildenafil while the parent drug only accounted for 47% of the plasma radioactivity after oral dosing.

Figure 48 below summarizes the metabolic pathways for sildenafil with the percentage of each metabolite in the urine and feces. There was no unchanged drug recovered in either urine or feces, indicating that the major clearance mechanism for sildenafil is metabolism. The major urinary metabolite was the aliphatic hydroxylated metabolite accounting for 41% of the urinary radioactivity (5.2% of the total dose). Urine contained a further 8 metabolites, accounting each for less than 1.5% of the dose. The major metabolite in feces was UK-150,564 and it accounted for 28% of radioactivity in the feces (22% of the dose). A further 16 metabolites were identified in feces, accounting each for less than 5% of the dose.

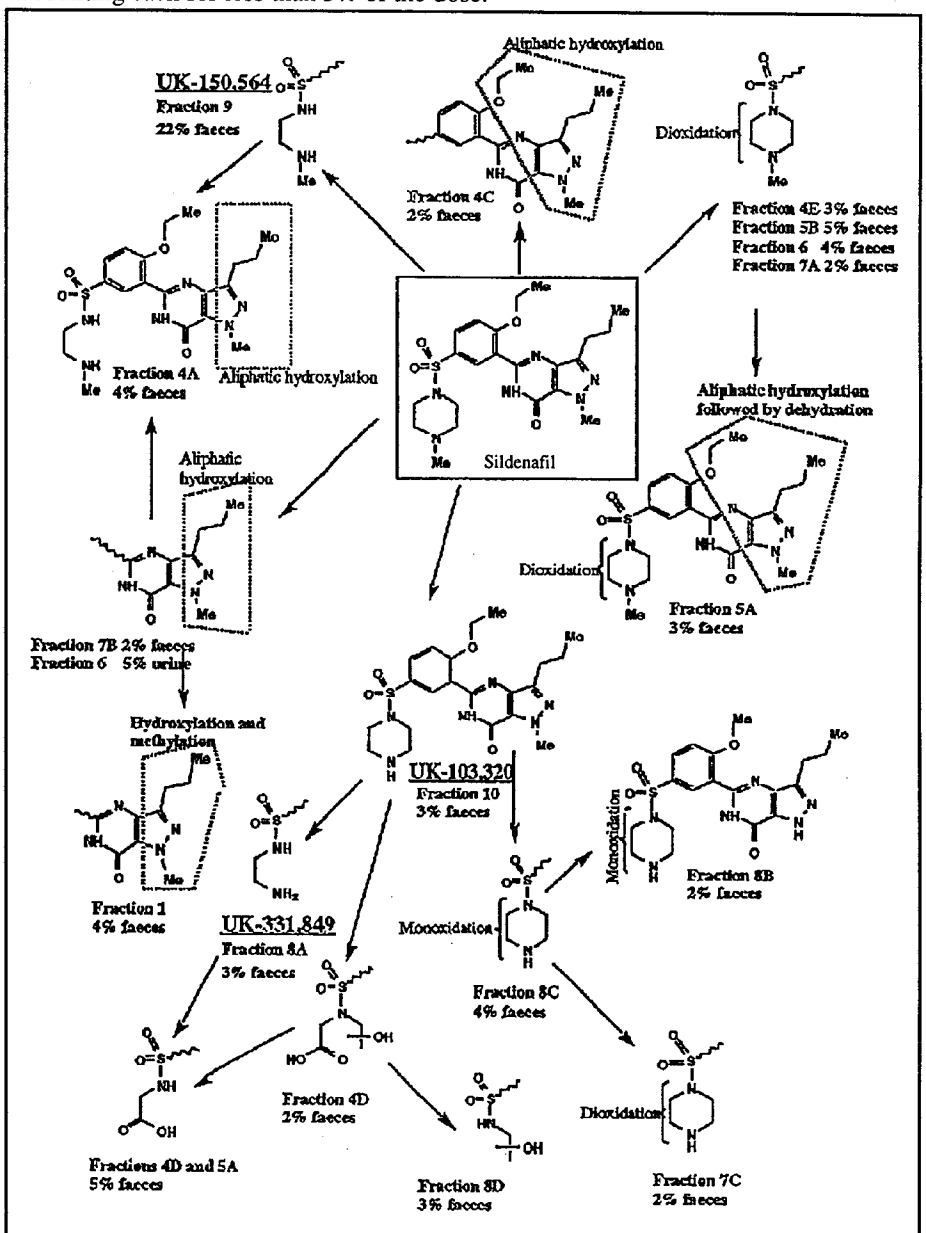

Figure 48. Proposed routes of metabolism for sildenafil (Study 148-215).

A22.6. Summary

The principle routes of metabolism of sildenafil were N-demethylation at the N-methyl piperazine and N-methyl pyrazole moieties, multiple oxidation and loss of a 2-carbon fragment from the piperazine ring, and aliphatic hydroxylation.