Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Appendix A5, page 92 through Appendix A9.6, page 103

A5. Study 148-002: Phase I open study to assess the potential of cimetidine to alter the pharmacokinetics of sildenafil (UK-92,480) in normal, healthy male subjects.

A5.1. Source documents

Study protocol NDA 20-895, vol 1.40; study report: NDA vol 1.40; electronic document: 46917592.pdf.

A5.2. Investigators

A5.3. Study dates

18 November 1995 to 29 January 1996.

A5.4. Study design

This study description was based upon the final study report, dated 2 May 1997.

The objective was to determine whether multiple-dose cimetidine administration alters the pharmacokinetics of sildenafil.

Drug supplies are shown in Table 60 below.

Table 60. Drug supplies (Study 148-002).

	Lot		Lot
Placebo for cimetidine	ED-G-222-891	Sildenafil 25 mg capsules	ED-S-347-994
Cimetidine (Tagamet)	7694T26		

A total of 20 health male volunteers, age 18 to 45, were to be recruited.

All subjects received a single oral dose of sildenafil 50 mg after overnight fast on day 1. On days 3 to 6, subjects received either double-blind placebo or cimetidine 800 mg. On day 5, subjects received randomized treatment followed 2 hours later by sildenafil 50 mg. Subjects fasted another 4 hours and refrained from caffeine after each drug administration.

Blood samples for determination of plasma levels of sildenafil and UK-103,320 were obtained on days 1 and 5 pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48 hours post-dose. Samples were collected in heparinized tubes, plasma was separated by centrifugation, and samples were stored at -20°C. Plasma levels of

Table 61 below.

Table 61. Assay for sildenafil and UK-103,320 (Study 148-002).

	Sildenafil		UK-103,320	
		Comment		Comment

C_{max}, AUC_{τ}, k_{el}, AUC, T_{max}, and $t_{1/2}$ were calculated.

Routine safety data were recorded.

A5.5. Results

A5.5.1. Conduct

Twenty-two subjects were randomized and treated. Two subjects withdrew after the first dose. Thus, 20 subjects, age 18 to 39, contributed data. Protocol violations appear to have been minor.

A5.5.2. Pharmacokinetics

Plasma levels of sildenafil and UK-103,320 are shown in Figure 26 below. Pharmacokinetic parameters are shown in Table 62 below.

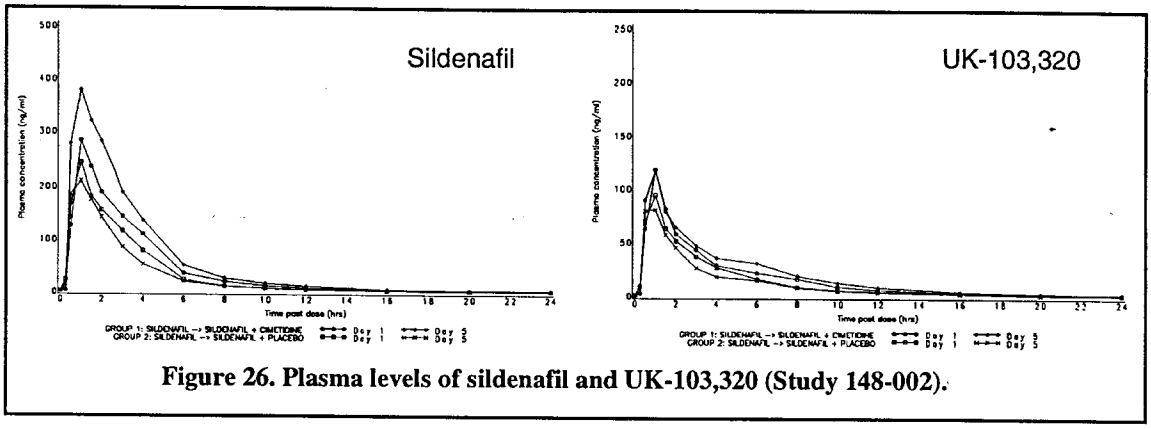

Figure 26. Plasma levels of sildenafil and UK-103,320 (Study 148-002).

Table 62. Pharmacokinetic parameters (Study 148-002).

	Sildenafil				UK-103,320			
	Placebo		Cimetidine		Placebo		Cimetidine	
	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
AUC (ng.h/mL)	716±260	605±174	889±246	1250±379	270±140	243±105	351±160	414±220
AUC_t (ng.h/mL)	666±271	598±174	883±245	1241±374	261±140	236±104	346±158	407±117
C_{max} (ng/mL)	250±105	220±58	283±69	383±111	98±42	88±30	111±42	115±51
T_{max} (h)	1.1±0.7	1.1±0.5	1.4±0.9	0.9±0.3	1.1±0.7	0.9±0.05	1.2±0.7	1.1±0.7
K_{el} (h^{-1})	0.27±0.09	0.27±0.03	0.23±0.05	0.20±0.05	0.18±0.03	0.22±0.05	0.21±0.06	0.18±0.04
$t_{1/2}$ (h)	2.6	2.6	3.0	3.5	3.9	3.2	3.3	3.9

A5.5.3. Safety

Two subjects withdrew consent (did not like venous puncture). No serious adverse events were reported. One subject had borderline CK elevation at baseline, and developed a substantial increase on day 2, and peaking on day 3 at about 60 times ULN (100% MM band). His CK diminished thereafter and he completed study about 6 weeks later. CK elevation was attributed to exercise.

A5.6. Summary

Cimetidine reduces gastric pH, potentially affecting bioavailability of sildenafil, and it is a non-specific inhibitor of cytochrome P450, potentially affecting the metabolism of sildenafil. The single-dose AUC and C_{max} for sildenafil increased about 50% when co-administered with cimetidine. Its metabolite, UK-103,320, was increased by about 30%. There was no effect of cimetidine on the elimination rate constants for sildenafil or UK-103,320, so the modest observed effect of cimetidine is apt to have been a result of alteration of absorption.

A6. Study 148-003: Phase I open study to assess the effect of concomitant antacid administration on the absorption of sildenafil (UK-92,480) in normal, healthy male subjects.

A6.1. Source documents

Study protocol NDA 20-895, vol 1.41; study report: NDA vol 1.41; electronic document: 46917205.pdf.

A6.2. Investigators

A6.3. Study dates

8 January 1996 to 12 February 1996.

A6.4. Study design

This study description was based upon the final study report, dated 9 June 1997.

The objective was to determine the effect of antacid administration on the absorption of a single dose of sildenafil.

Drug supplies are shown in Table 63 below.

Table 63. Drug supplies (Study 148-003).

	Lot
Sildenafil 25 mg capsules	ED-S-347-994

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

This was an open-label, two-way crossover study in which subjects received single oral doses of sildenafil 50 mg on study days separated by at least 14 days. In random order, on one of the study days, subjects received Maalox® 30 ml just prior to administration of sildenafil. All dosing was done after overnight fasting and fasting continued for 4 hours after dosing.

Blood samples for determination of plasma levels of sildenafil and UK-103,320 were obtained on days 1 and 5 pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48 hours post-dose. Samples were collected in heparinized tubes, plasma was separated by centrifugation, and samples were stored at -20°C. Plasma levels of

Table 64 below.

Table 64. Assay for sildenafil and UK-103,320 (Study 148-003).

	Sildenafil		UK-103,320	
	LLQ	Comment	LLQ	Comment

C_{max}, AUC_{τ}, k_{el}, AUC, T_{max}, and $t_{1/2}$ were calculated.

Routine safety data were recorded.

A6.5. Results

A6.5.1. Conduct

Twelve subjects were randomized and treated. Protocol violations appear to have been minor.

A6.5.2. Pharmacokinetics

Plasma levels of sildenafil and UK-103,320 are shown in Figure 27 below. Pharmacokinetic parameters are shown in Table 65 below.

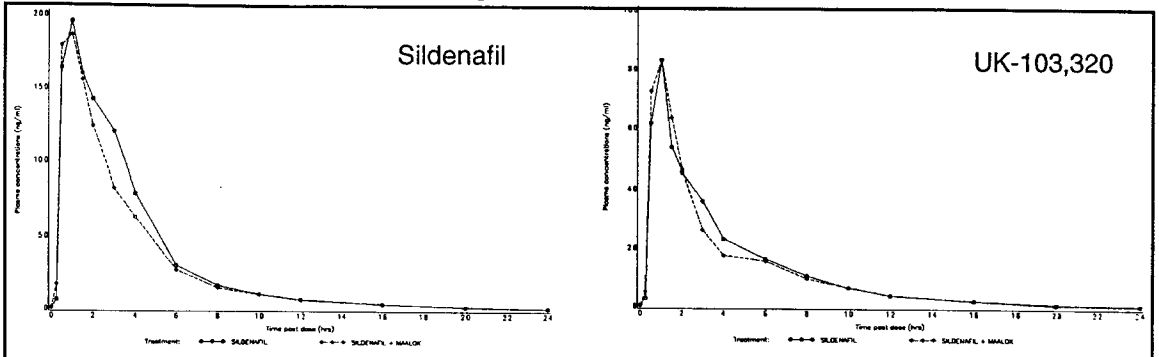

Figure 27. Plasma levels of sildenafil and UK-103,320 (Study 148-003).

Table 65. Pharmacokinetic parameters (Study 148-003).

	Sildenafil		UK-103,320	
	Nothing	Maalox	Nothing	Maalox
AUC (ng.h/mL)	700±198	627±164	272±76	259±75
AUC_t (ng.h/mL)	693±197	621±163	265±75	252±76
C_{max} (ng/mL)	238±86	238±106	96±37	100±31
T_{max} (h)	1.2±0.8	0.8±0.4	1.1±0.7	0.8±0.4
K_{el} (h^{-1})	0.22±0.02	0.23±0.05	0.22±0.05	0.21±0.02
$t_{1/2}$ (h)	3.1	3.0	3.2	3.3

A6.5.3. Safety

There was one case of syncope associated with phlebotomy. There were no serious adverse events. Seven subjects reported penile erections.

A6.6. Summary

Plasma levels of sildenafil and its primary metabolite, UK-103,320, were unaffected by Maalox. The study appears to have been powered adequately to detect a 50% change in AUC or C_{max}.

A7. Study 148-004: Phase I investigator-blind, placebo-controlled, evaluation of safety, toleration, and pharmacokinetics of sildenafil following escalating single oral doses in healthy male volunteers.

A7.1. Source documents

Study protocol NDA 20-895, vol 1.42; study report: NDA vol 1.42; electronic document: 46314080.pdf.

A7.2. Investigators

Single-center study with 1 investigator in the US.

A7.3. Study dates

9 December 1996 to 9 January 1997.

A7.4. Study design

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

Drug supplies are shown in Table 66 below.

Table 66. Drug supplies (Study 148-004).

	Lot		Lot
Placebo	N5275-G1	Sildenafil 100 mg	N6064-G1

A total of 20 health male volunteers, age 40 to 65, were to be recruited.

Two cohorts of 10 subjects were to receive single ascending doses of sildenafil or placebo in a 4:1 randomization. Planned doses were 100, 200, 400, and 800 mg. Because of effects on blood pressure observed at 200 mg, the actual doses used were 100, 200, 300, 400, 600, and 800 mg. Doses were administered with water after overnight fast. Data collected were vital signs, ECGs, and plasma drug levels. Pharmacokinetic sampling was at 0 (pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 32, 40 and 48 hours post-dose. Drug levels were determined by

detection.

Routine safety data were recorded.

A7.5. Results

A7.5.1. Conduct

Twenty subjects were randomized and treated. The mean age was 53 years. All but 3 were Caucasian.

Few subjects had standing vital signs measured at doses over 200 mg. Other protocol violations appear to have been minor.

A7.5.2. Pharmacokinetics

Mean plasma levels of sildenafil and metabolite UK-103,320 are shown in Figure 28 below. Table 67 below shows all available pharmacokinetic parameters. C_{max} and AUC increased more than proportionally with dose, as shown in Figure 29 below.

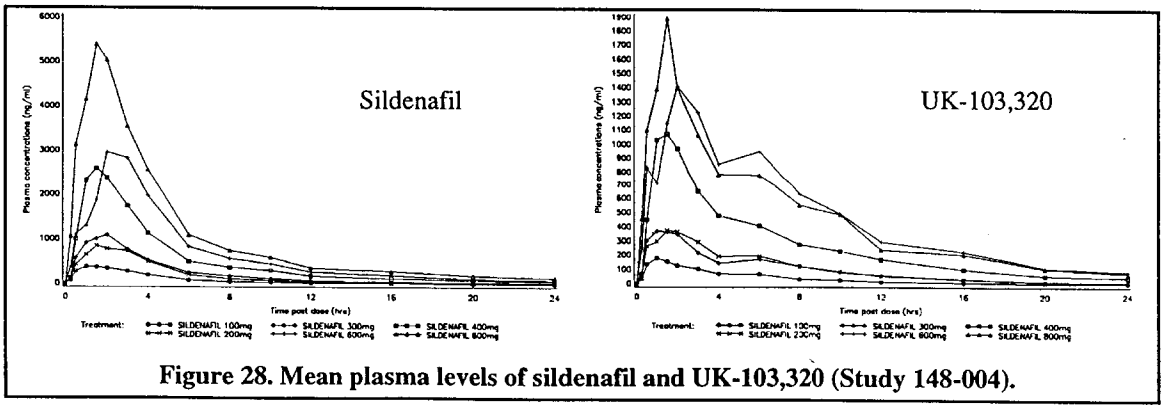

Figure 28. Mean plasma levels of sildenafil and UK-103,320 (Study 148-004).

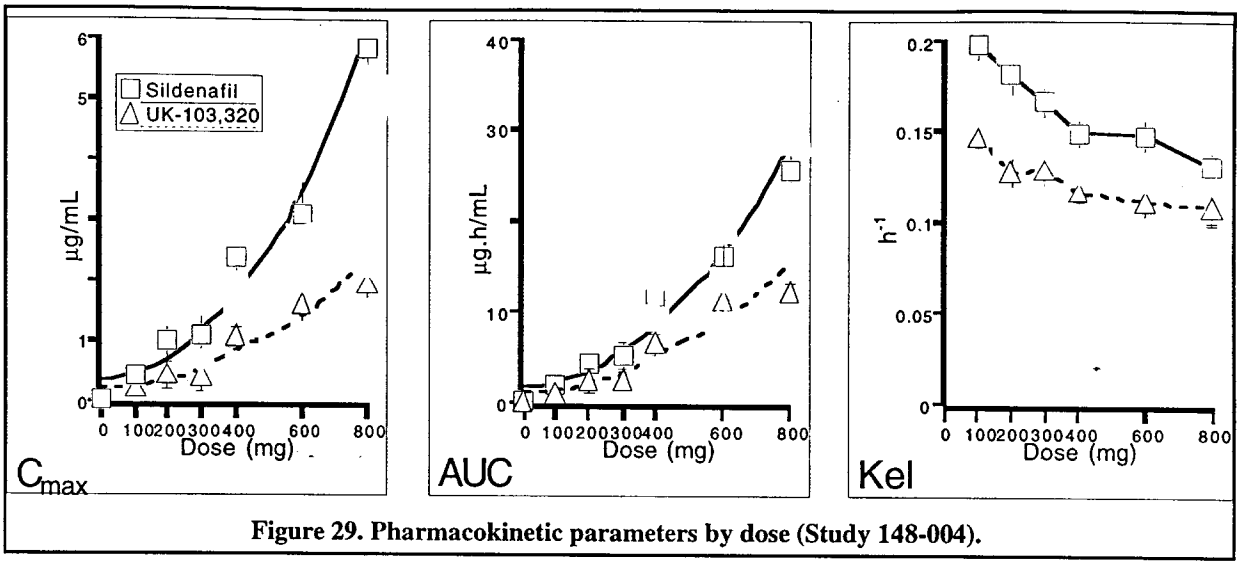

Figure 29. Pharmacokinetic parameters by dose (Study 148-004).

Table 67. Pharmacokinetic parameters (Study 148-004).

	Sildenafil (mg)						UK-103,320 (mg)					
	100 N=8	200 N=8	300 N=4	400 N=4	600 N=4	800 N=4	100 N=8	200 N=8	300 N=4	400 N=4	600 N=4	800 N=4
AUC (ng.h/mL)	1691	4088	5156	11588	16114	25686	834	2392	2351	6531	11274	12095
AUC_τ (ng.h/mL)	1682	4081	5142	11578	16079	25611	826	2378	2342	11569	11213	12029
C_{max} (ng/mL)	411	1001	1081	2367	3084	5834	201	430	391	1066	1590	1939
T_{max} (h)	1.4	2.2	2.1	1.4	2.5	1.8	1.1	1.8	1.4	1.1	2.4	1.5
K_{el} (h^{-1})	0.20	0.18	0.17	0.15	0.15	0.13	0.15	0.13	0.13	0.12	0.11	0.11
$t_{1/2}$ (h)	3.5	3.8	4.2	4.7	4.7	5.3	4.8	5.5	5.4	6.0	6.2	6.5

Effects of the 800-mg dose on sitting vital signs (double differences from placebo and baseline) are shown in Figure 30 below. Somewhat larger and more sustained effects on blood pressure were observed with the 600-mg dose. The study was too small and the intra-subject variability too great to make a hysteresis plot useful.

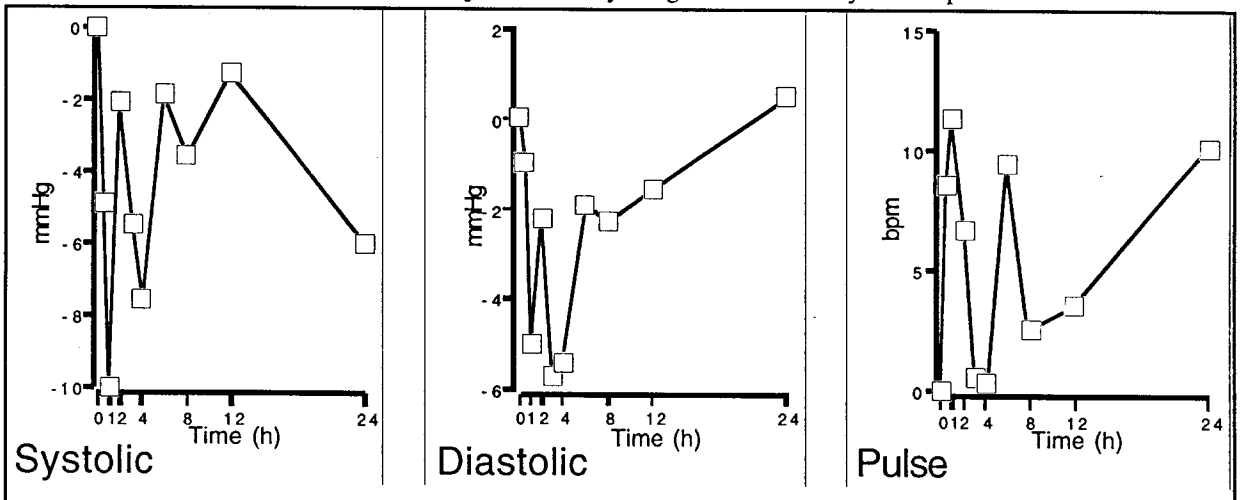

Figure 30. Pharmacodynamic effects at 800 mg, while standing (Study 148-004).

A7.5.3. Safety

Adverse events were reported by all but one subject at doses >100 mg. There were two cases described as severe dizziness, one of which was associated with syncope.

Visual disturbances were reported by about half of the subjects at doses >100 mg. The frequency of such reports did not trend upwards with dose, but the duration of events increased from 0.25 to 1.4 hours at doses up to 400 mg and 2.5 to 8 hours at higher doses. The effects were described as difficulty seeing in dim light, color aberration, and color tinges. Effects tended to be seen near the expected time of peak plasma concentration.

About half of the subjects at 100 and 200 mg reported erections. The rate was less at higher doses, but one subject on 600 mg reported an erection lasting 5 hours.

A variety of minor laboratory abnormalities were reported. None were serious or had any apparent relationship to treatment.

Inspection of line listings of ECG parameters revealed no treatment-related trends or significant outliers.

A7.6. Summary

Single doses of sildenafil >200 mg were associated with greater-than-proportional increases in C_{max} and AUC for both sildenafil and its major metabolite, consistent with some saturable binding or elimination step. At about the time of peak sildenafil levels in plasma, there are substantial reductions in sitting and standing blood pressure and a compensatory increase in heart rate. The time course was not well characterized here, but it produces symptomatic effects at doses >200 mg and it probably lasts several hours. Effects attributable to inhibition of retinal phosphodiesterase appeared at doses >100 mg.

A8. Study 148-101/101B: A randomised, double-blind, placebo controlled, parallel-group, fixed-dose, multicentre, long-term dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered prior to sexual activity to male patients with erectile dysfunction.

A8.1. Source documents

Study protocol NDA 20-895, vol 1.104; study report: NDA vol 1.104; electronic document: 47100356.pdf.

A8.2. Investigators

Multi-center study with 22 investigators in the United States.

A8.3. Study dates

30 June 1995 to 1 May 1996.

A8.4. Study design

This study description was based upon the protocol dated 19 May 1995. There were no amendments.

Drug supplies are shown in Table 68 below.

Table 68. Drug supplies (Study 148-101/101B).

	Lot		Lot
Placebo 5 mg	ED-S-072-295	Sildenafil 5 mg	ED-S-106-395
Placebo 25 mg	ED-S-073-295	Sildenafil 25 mg	4469-005-GI ED-S-074-295 ED-S-239-795 ED-S-240-795 ED-S-343-995

The intent was to randomize 375 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) spinal cord injury, (3) regular use of nitrates, estrogens, anti-androgens, anticoagulants, or psychotropic drugs, (4) history of hematologic, renal, or hepatic disease, (5) stroke or myocardial infarction within 6 months, (6) life-threatening cardiac arrhythmia or coronary artery disease, (7) migraine or cluster headache, (8) history of depression or major psychiatric disorder, (9) history of bleeding disorder or active peptic ulcer disease, (10) suspected sexually transmitted disease, (11) postural hypotension, or blood pressure outside 90/50 to 160/95 mmHg, (12) other experimental drug use within 4 weeks, (13) alcohol or drug dependence, or (14) recent blood donation.

At the end of a 4-week treatment-free run-in period during which baseline sexual performance data were collected, subjects were randomized to placebo or sildenafil 5, 25, 50, or 100 mg and followed for 8 weeks with follow-up at 2-week intervals. Subjects were instructed to take study drug approximately one hour before planned sexual activity, not more than once per day. Subjects completed an event log noting time of study drug administration and subsequent sexual activity. Subjects completed a sexual function questionnaire, and partners completed a separate questionnaire.

Subjects who completed the first 8 weeks of double-blind treatment were eligible to continue double-blind treatment for an additional 16 weeks (protocol 148-101B).

The primary efficacy assessment was at week 8. The primary end point was the ability to achieve an erection during sexual activity, as retrospectively assessed by the response toquestion 1 of the sexual function questionnaire.

Safety assessments included (1) ECGs at screening and week 8, (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.

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

A8.5. Results

A8.5.1. Conduct

Five hundred and twenty-three subjects were screened, 416 were randomized, and 359 (86%) completed study.

Demographics of the 2 treatment groups are shown in Table 69 below. About 38% of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 11% had used non-drug treatments.

Table 69. Demographics (Study 148-101/101B).

		Placebo N=83	Sildenafil 5 mg N=86	Sildenafil 25 mg N=82	Sildenafil 50 mg N=83	Sildenafil 100 mg N=82
Race (%)	White	90	93	88	89	85
	Black	7.2	5.8	7.3	7.2	13
	Other	2.4	1.2	4.9	3.6	1.2
Age	Mean	58	58	57	56	59
	Range	36-79	26-80	32-79	35-73	37-79
Etiology (%)	Organic	76	80	70	70	74
	Psychogenic	7	5	12	7	10
	Mixed	17	15	18	23	16
Duration (y)	Mean	5.1	5.1	4.2	3.8	4.9
Med hx (%)	Diabetes	14	15	8.5	18	20
	Hypertension	33	31	30	34	38
	IHD	7.2	4.7	6.1	8.4	6.1
	Periph vasc dis	0	0	2.4	1.2	1.2
	Depression	1.2	1.2	1.2	0	0
	Prostatectomy	3.6	7.0	3.7	2.4	4.9

Protocol violations are described in Table 70 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 70. Protocol violations (Study 148-101/101B).

At randomization	n	On treatment	n
Concomitant meds	19	>1 dose per day	52
Lab abnormalities	8	Other ED treatment	12
Penile anatomical defect	6	Concomitant meds	7
Confounding medication	5	Blind broken for AE	1
Self-injection during single-blind	4		
Active medical problems	3		
Other	9		
Total[a]	53	Total	52

a. Some subjects had more than one violation.

Nineteen percent of subjects on placebo and 12% of subjects on sildenafil discontinued. One to two subjects per group discontinued for lack of efficacy.

A8.5.2. Effectiveness

Eleven to 22 subjects per group were excluded from evaluation for effectiveness, generally because the week-8 data were not returned. All randomized subjects with a post-randomization assessment were included in the sponsor's ITT analyses. Responses to EF question 1 (ability to attain an erection) were scored as 0 for no

attempts, 1 for never or rarely successful, etc., up to 5 for always or almost always successful. The sponsor's results are summarized in Table 71 below.

Table 71. ITT analyses of EF question 1 (Study 148-101/101B).

		Placebo N=83		Sildenafil 5 mg N=86		25 mg N=82		50 mg N=83		100 mg N=82		*P*
		n	Q	n	Q	n	Q	n	Q	n	Q	
How often were you able to get erection?	Baseline	—	1.8[a]	—	—	—	—	—	—	—	—	
	Week 8	78	2.1	81	2.7	81	3.1	81	3.5	77	3.7	<0.0001
	Week 24	78	2.1	81	2.7	81	2.9	81	3.1	77	3.6	<0.0001

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

There were monotonic, dose-related increases in the proportion of subjects who said treatment had improved their erections at week 8 and week 24. With the exception of questions pertaining to sexual desire, there were highly significant treatment effects for all sexual function questionnaire elements. Ninety-four percent of partners responded to the partner questionnaire at weeks 8 and 24, with increasing partner satisfaction with dose at both of these time points. The proportion of successful attempts at intercourse, as determined from the event logs, increased monotonically by dose.

The reviewers performed no analyses of these data.

A8.5.3. Safety

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

A8.6. Summary

The population included subjects with erectile dysfunction of organic etiology, but not spinal cord injury. Although not analyzed extensively by the reviewers, the results of the sponsor's assessments of erectile function and sexual performance were highly internally consistent and also consistent with later studies with sexual performance as a primary end point. The LOCF analyses were not useful for assessing the degree to which treatment effects were sustained for the period of study.

A9. Study 148-101C: An open, non-comparative study to assess the long-term safety of sildenafil in patients with erectile dysfunction.

A9.1. Source documents

Study protocol NDA 20-895, vol 1.130; study report: NDA vol 1.130; electronic document: 46916369.pdf.

A9.2. Investigators

Multi-center study with 22 investigators in the United States.

A9.3. Study dates

11 January 1996 to 21 January 1997.

A9.4. Study design

This study description was based upon the protocol amendment dated 21 June 1996. This amendment increased the duration of open-label study from 28 to 36 weeks.

Drug supplies are shown in Table 72 below.

Table 72. Drug supplies (Study 148-101C).

	Lot
Sildenafil 25 mg	4469-005-G1 4469-006-G1 4469-0008-G1 ED-S-343-995

Subjects were all previous participants in Study 148-101/101B[1]. Subjects must have completed the blinded study without a serious adverse event possibly related to study drug.

Visits were scheduled at 2, 4, 8, 12, 20, and 28 weeks. Subjects could have their doses adjusted between 25 and 100 mg. The primary end point was whether subjects were satisfied with the effect of treatment. Subjects also kept an event log.

Routine safety data were collected.

A9.5. Results

A9.5.1. Conduct

Three hundred and thirty-seven subjects (94% of subjects completing the previous study) entered long-term open-label study, and 269 (80%) completed study.

Subject demographics were similar to those in Study 148-101/101B. The mean age was 57. The mean duration of erectile dysfunction was 5 years. Etiology of erectile dysfunction was described as organic in 72%, psychogenic in 8.6%, and mixed in 19%. Eighty-two percent of subjects had received sildenafil for 24 weeks during the previous study.

A variety of protocol violations in Study 148-101/101B should have precluded participation in the open-label study.

Twenty percent of subjects discontinued. Reasons for discontinuation included lack of effectiveness (8.6%, mostly titrated to the highest allowed dose) and adverse events or laboratory abnormalities (5%).

Exposure is characterized in Figure 31 below. The proportion of subjects exposed for different periods of time is shown in the left panel. The proportion of subjects receiving different ranges of number of doses is shown in the center panel. The proportion of subjects receiving each dose level is shown in the right panel.

[1] *Study 148-101/101B: A randomised, double-blind, placebo controlled, parallel-group, fixed-dose, multicentre, long-term dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered prior to sexual activity to male patients with erectile dysfunction.* on page 99.

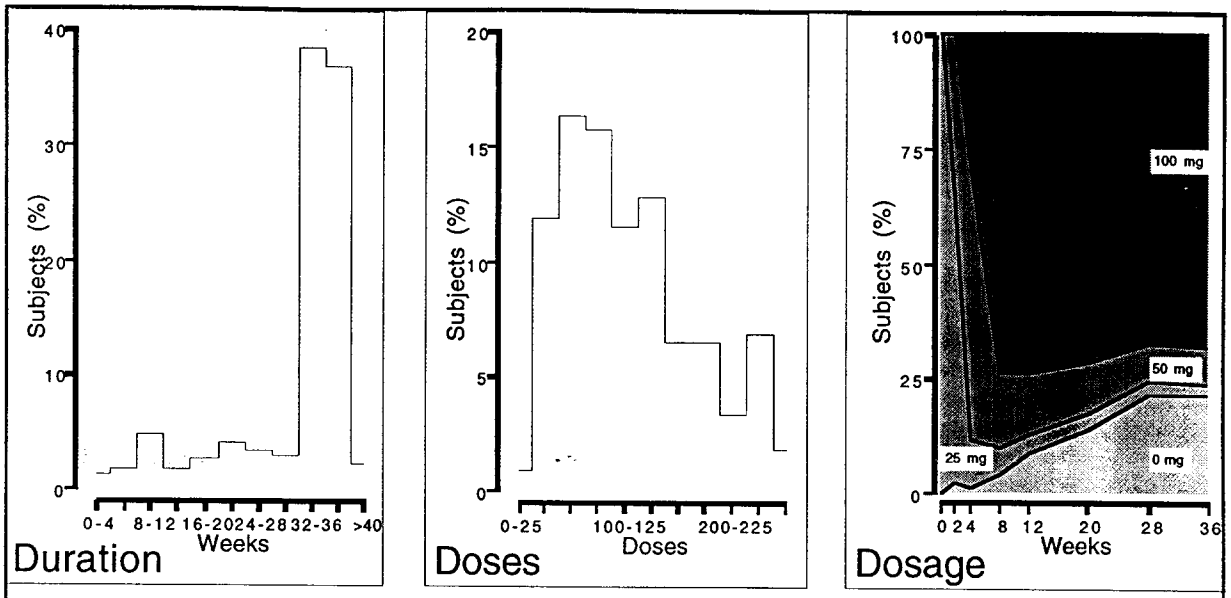

Figure 31. Exposure to study drug (Study 148-101C).

A9.5.2. Effectiveness

By the sponsor's analyses, the number of subjects expressing satisfaction with the treatment rose from 10% at 2 weeks, when essentially all were receiving 25 mg, to 90% at the study end, when most subjects were on 100 mg. The reviewers performed no analyses of these data.

A9.5.3. Safety

Safety will be reviewed for all open-label studies together.

A9.6. Summary

Roughly 80% of subjects had some exposure to sildenafil for 6 months prior to enrollment in this study, so the actual withdrawal rate here is somewhat lower than could be expected in a naive population. Few subjects remained on 25 or 50 mg when given the opportunity to move to a higher dose.