

Center for Drug Evaluation and Research

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Appendix A34, page 170 through Appendix A43.6, page 190

A34. Study 148-229: A double-blind, randomised, single oral dose, four period, two-way crossover pilot study to investigate the acute effects of sildenafil on sperm motility.

- A34.1. Source documents** Study protocol NDA 20-895, vol 1.74; study report: NDA vol 1.74; electronic document: 47111402.pdf.
- A34.2. Investigators** Single-center study with 1 investigator in Norway.
- A34.3. Study dates** 20 August 1996 to 14 October 1996.
- A34.4. Study design** This study description was based upon the final study report, dated 7 August 1997.
- A34.4.1. Objectives**
- To determine the acute effects of sildenafil (100 mg) on sperm motility (percentage motile, static, rapid, progressive, progressive motility and mean lateral head displacement) in healthy male subjects.
 - To determine the acute effects of sildenafil on sperm count, sperm density, sperm morphology, and vitality, ejaculate volume and viscosity in healthy male subjects.
 - To determine sildenafil and UK-103,320 concentrations in ejaculate and to compare these with plasma concentrations.
 - To assess the safety and toleration of a single dose of sildenafil (100 mg) in healthy male subjects.
- A34.4.2. Formulation** Sildenafil 100 mg tablets were from lot 4469-115. Matching placebo tablets were from lot 4469-084.
- A34.4.3. Population** A total of 16 normal volunteers, age 18 to 45, were to be recruited.
- A34.4.4. Procedures**
- On each of four clinic days separated by 7 days, subjects received single oral doses of placebo or sildenafil 100 mg at least 2 hours after the last meal. Semen samples were collected at 1.5 and 4 hours after dosing.
- Semen samples were assessed for sperm motility, count, density, morphology, and vitality. Ejaculate volume and viscosity were also assessed.
- Blood samples for assay of plasma levels of sildenafil and UK-103,320 were taken at baseline, 0.25, 0.5, 1, 2, 3, 4, and 6 hours after dosing.
- Routine safety data were recorded.
- A34.4.5. Assay**
- A34.4.6. Analysis** Pharmacokinetic parameters were calculated using standard non-compartmental techniques. The relationships between the total amounts of sildenafil or UK 103,320 in the semen and the corresponding total and free plasma concentrations were investigated using linear regression analyses.

A34.5. Results

A34.5.1. Conduct

Seventeen subjects were randomized and 16 completed study. One subject discontinued for back pain and urinary retention, and was replaced¹. There were minor protocol deviations, but no subject was excluded from analyses.

A34.5.2. Pharmacokinetics

Mean plasma concentration-time profiles for sildenafil and UK-103,320 are shown in Figure 59 below and the corresponding parameters are summarized in Table 125 below.

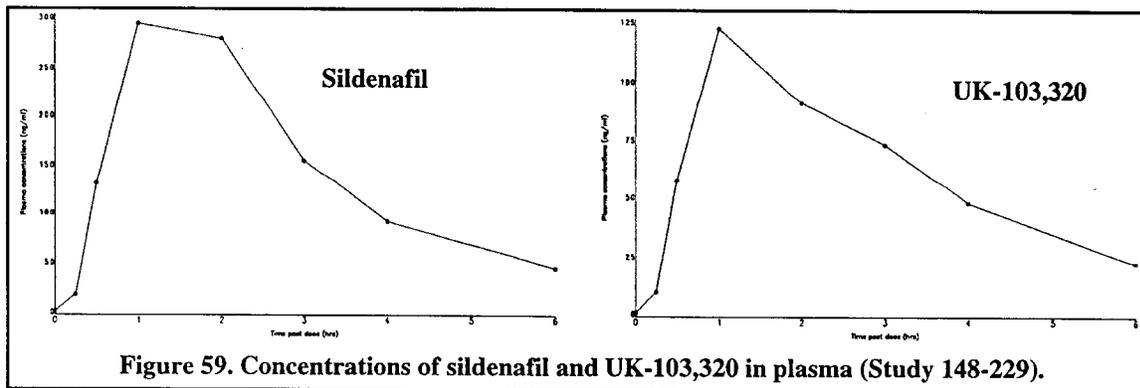


Figure 59. Concentrations of sildenafil and UK-103,320 in plasma (Study 148-229).

Table 125. Pharmacokinetic parameters (Study 148-229).

	Sildenafil	UK-103,320		Sildenafil		UK-103,320	
				1-2 h	4 h	1-2 h	4 h
Plasma AUC ₆ (ng.h/mL)	841	341	Plasma binding (%free)	5.7	4.7	6.9	5.5
Plasma C _{max} (ng/mL)	331	125	Total plasma conc (ng/mL)	286	91	106	47
Plasma T _{max} (h)	1.4	1.4	Free plasma conc (ng/mL)	15	4.2	7.0	2.5
Total in semen (ng)	188	18	Semen conc (ng/mL)	51	16	5.1	7.1

Figure 60 below shows the mean semen concentration-time profiles for both sildenafil and its metabolite with the corresponding parameters summarized in Table 125. The mean semen sildenafil concentrations were approximately 18% of the plasma concentrations at the same time points. However, the same trend was not observed for UK 103,320. The mean semen concentrations were approximately 5 and 15% of the plasma concentrations. Figure 61 below shows the relationship between the concentration or amount in the semen and the total plasma concentrations for both sildenafil and UK 103,320.

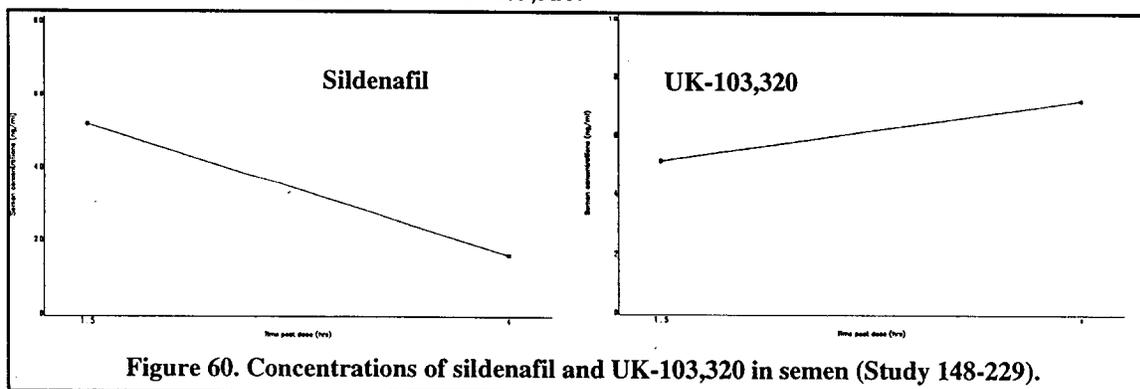
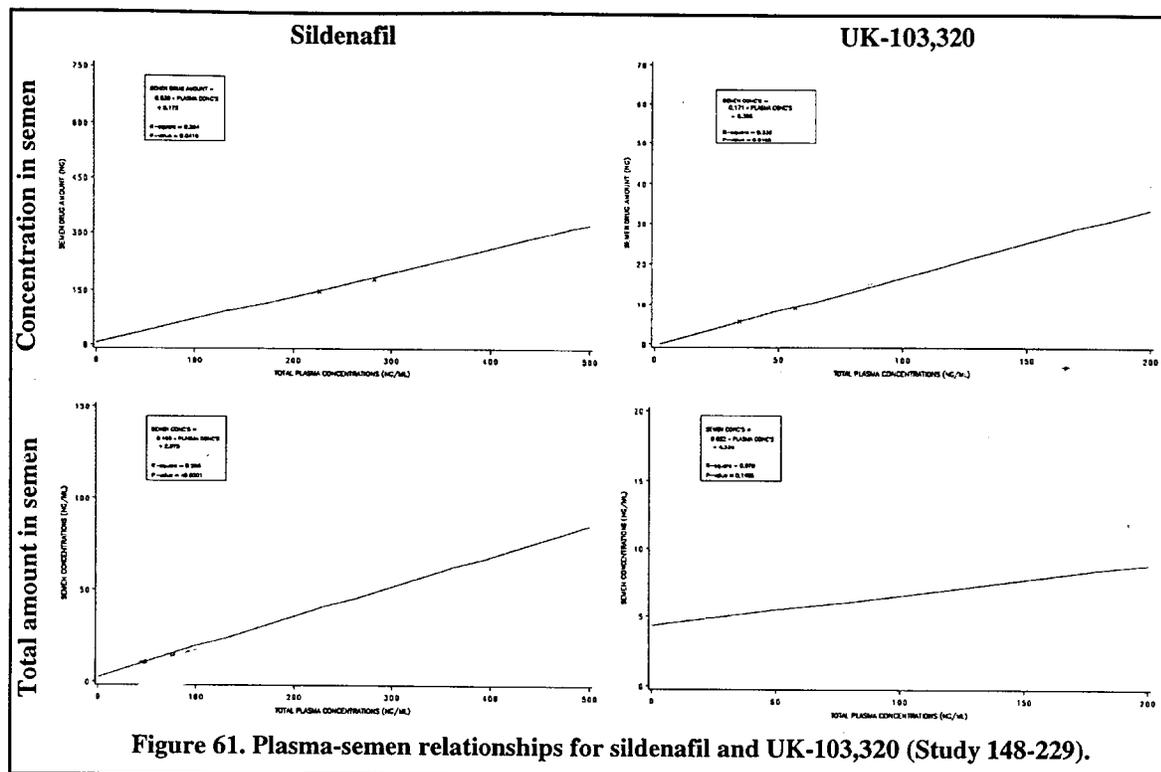


Figure 60. Concentrations of sildenafil and UK-103,320 in semen (Study 148-229).

¹. Adverse event noted after first study period. The subject had received placebo.



The relationship between the amount of sildenafil and metabolite and the corresponding total concentrations was statistically significant ($p < 0.05$). Moreover, there was a highly statistically significant relationship between sildenafil and metabolite semen concentrations and either free or total plasma concentrations of either sildenafil or metabolite ($p < 0.001$).

A34.5.3. Pharmacodynamics

Sperm motility parameters remained within the normal range of the laboratory and showed no mean differences between placebo and sildenafil periods. Ninety-five percent confidence limits on the difference was typically $< 10\%$. Similar results with similar confidence limits were obtained for sperm count, density, morphology, and vitality, and for ejaculate volume and viscosity.

A34.5.4. Safety

There were no serious or treatment-related severe adverse reactions. Adverse events overall were more common on sildenafil, with headache, vasodilation, and penile erection most notable on sildenafil. Three subjects reported color-related visual disturbances, all shortly after exposure to sildenafil.

A34.6. Summary

The study was adequately powered to detect small effects on sperm motility, count, etc., probably below levels of clinical significance. No such effects were found in response to single doses of sildenafil 100 mg. The sildenafil concentration in semen was 18% of the total plasma concentration at 1.5 and 4 hours post-dose, while the concentration of UK-103,320 in semen was 5% (1.5 hours) and 15% (4 hours) of the corresponding plasma levels. The effects of recurrent exposure were not assessed.

Study 148-230: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking isosorbide mononitrate oral therapy.

NDA 20-895
Sildenafil for male impotence

A35. Study 148-230: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking isosorbide mononitrate oral therapy.

A35.1. Source documents Study protocol NDA 20-895, vol 4.1; study report: NDA vol 4.1; electronic document: 46505263.pdf.

A35.2. Investigators Single-center study with 1 investigator in the UK.

A35.3. Study dates 16 December 1996 to 16 April 1997.

A35.4. Study design This study description was based upon the final study report, dated 21 November 1997.

The objective was to determine the effect of a single 50-mg dose of sildenafil on vital signs in subjects receiving chronic nitrates.

A total of 16 subjects age 18 to 75, with chronic stable angina, on nitrate therapy, were to be recruited. Exclusions were made for (1) myocardial infarction, (2) exercise-induced angina, (3) blood pressure outside 100/60 to 170/100 mmHg, (4) orthostatic hypotension (>10 mmHg decrease or symptoms), (5) other significant baseline abnormalities, and (6) excessive alcohol consumption.

Subjects switched their baseline nitrate to isosorbide mononitrate 20 mg 5 to 7 days prior to the first study day. In randomized order on study days at least 7 days apart, subjects received isosorbide mononitrate 20 mg plus placebo or sildenafil 50 mg.

Vital sign assessments were made sitting and standing -0.25, 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, and 6 hours after dosing.

Routine safety data were recorded.

A35.5. Results

A35.5.1. Conduct Eighteen subjects age 45 to 78 years were randomized and all but one completed both study phases. There were minor protocol deviations.

A35.5.2. Pharmacodynamics Vital sign data are shown in Table 126 below, as analyzed by the sponsor. Differences in blood pressures between treatment groups were all highly statistically significant.

Table 126. Vital signs (Study 148-230).

	MaxΔ Systolic		MaxΔ Diastolic		MaxΔ Pulse	
	Placebo N=17	Sildenafil N=18	Placebo N=17	Sildenafil N=18	Placebo N=17	Sildenafil N=18
Sitting	-22	-41	-13	-26	14	16
Standing	-25	-52	-15	-29	17	19

The time courses of group-mean standing blood pressure changes from baseline are shown in Figure 62 below. Changes in sitting blood pressure were similar. There was a 5-bpm greater increase in pulse rate on sildenafil sustained for the first 3 hours after dosing, as shown in Figure 63 below.

Study 148-230: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking isosorbide mononitrate oral therapy.

NDA 20-895
Sildenafil for male impotence

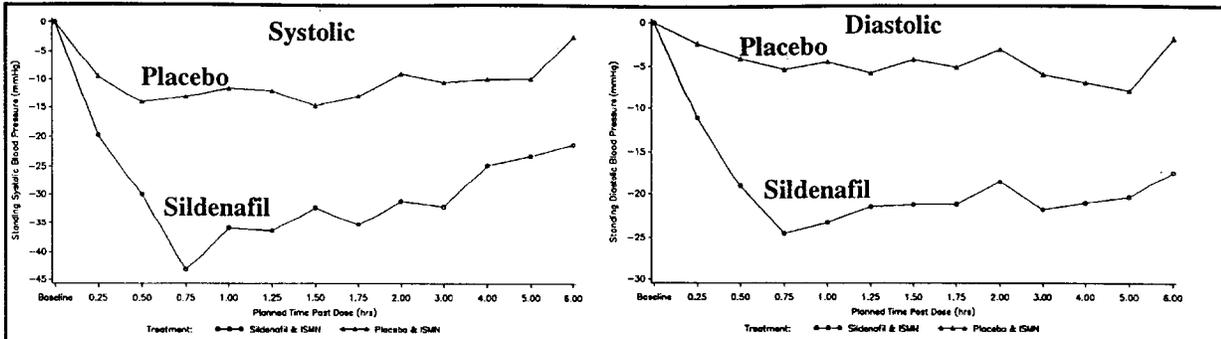


Figure 62. Changes in standing blood pressure (Study 148-230).

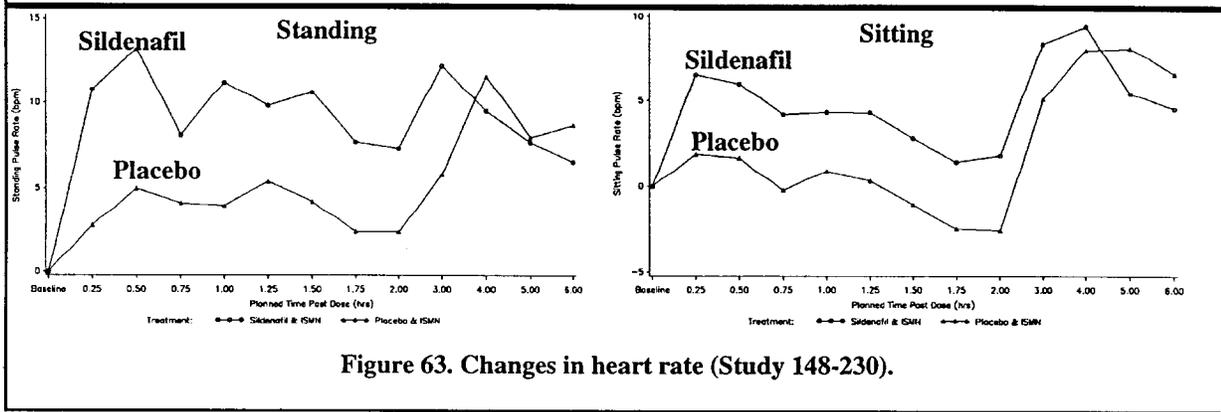


Figure 63. Changes in heart rate (Study 148-230).

A35.5.3. Safety

There were no serious adverse events and no discontinuations for adverse events. Five subjects on sildenafil and 2 subjects on placebo dizziness that probably represented symptomatic hypotension.

A35.6. Summary

Sildenafil substantially decreased blood pressure for more than 6 hours and increased heart rate for about 3 hours when co-administered with isosorbide mononitrate, often to the point of being symptomatic.

Study 148-231: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking sublingual glyceryl trinitrate (GTN) therapy.

NDA 20-895
Sildenafil for male impotence

A36. Study 148-231: A double blind, placebo controlled, randomised, two way crossover study to investigate the effects of a single dose of sildenafil (50mg) in patients with stable angina taking sublingual glyceryl trinitrate (GTN) therapy.

A36.1. Source documents Study protocol NDA 20-895, vol 4.2; study report: NDA vol 4.2; electronic document: 44785859.pdf.

A36.2. Investigators Multi-center study with 2 investigators in the UK.

A36.3. Study dates 10 March 1997 to 3 July 1997.

A36.4. Study design This study description was based upon the final study report, dated 21 November 1997.

The objective was to determine the effect of a single 50-mg dose of sildenafil on vital signs in subjects receiving glyceryl trinitrate.

A total of 16 subjects age 18 to 75, with chronic stable angina, on prn nitroglycerin therapy, were to be recruited. Exclusions were made for (1) myocardial infarction, (2) exercise-induced angina, (3) blood pressure outside 100/60 to 170/100 mmHg, (4) orthostatic hypotension (>10 mmHg decrease or symptoms), (5) other significant baseline abnormalities, and (6) excessive alcohol consumption.

Subjects were to have taken no nitrates other than prn sublingual nitroglycerin for 14 days prior to the first study day. In randomized order on study days at least 7 days apart, subjects received glyceryl trinitrate 0.5 mg plus placebo or sildenafil 50 mg.

Vital sign assessments were made sitting and standing -0.25, 0, 0.25, 0.5, 0.75, and 1 hour, then every 3 minutes out to 2 hours, and 2.25, 2.5, 2.75, 3, 4, 5, and 6 hours after dosing.

Routine safety data were recorded.

A36.5. Results

A36.5.1. Conduct

Sixteen subjects age 47 to 77 years were randomized and all but one completed both study phases. There were minor protocol deviations.

A36.5.2. Pharmacodynamics

Vital sign data are shown in Table 127 below, as analyzed by the sponsor. Differences in blood pressures between treatment groups were all highly statistically significant.

Table 127. Vital signs (Study 148-231).

	MaxΔ Systolic		MaxΔ Diastolic		MaxΔ Pulse	
	Placebo N=15	Sildenafil N=16	Placebo N=15	Sildenafil N=16	Placebo N=15	Sildenafil N=16
Sitting	-26	-36	-11	-21	10	16

The time courses of group-mean sitting vital sign changes from baseline are shown in Figure 64 below.

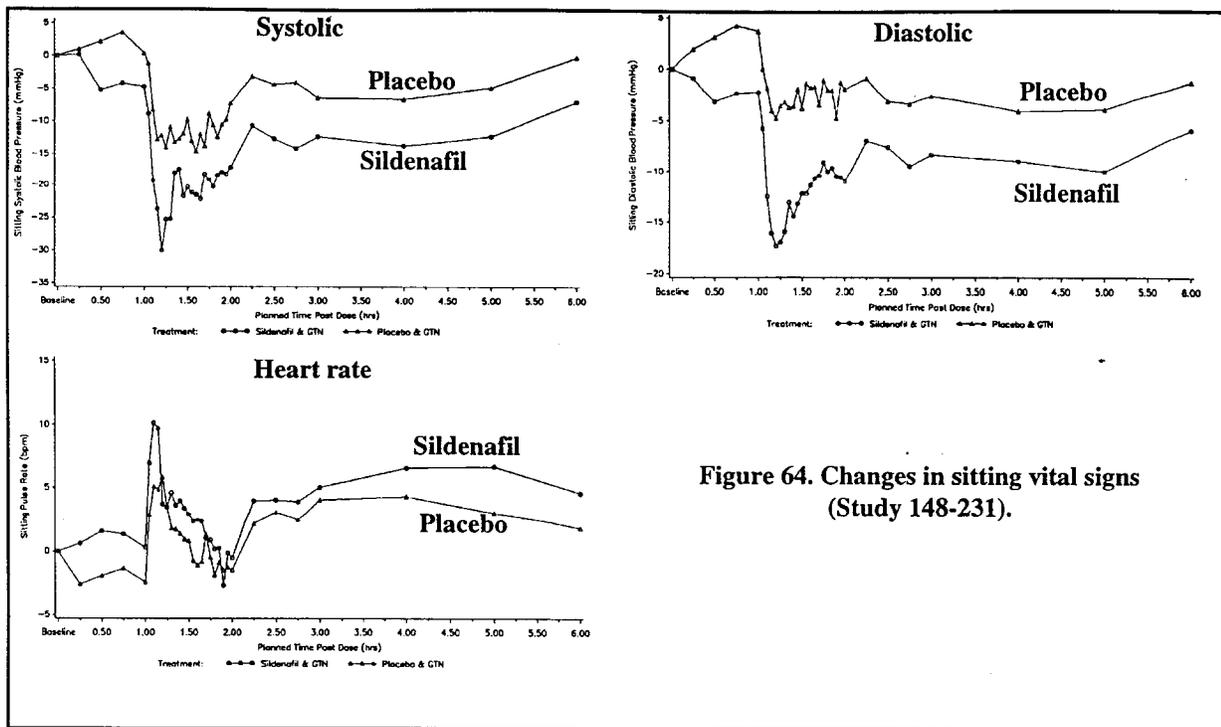


Figure 64. Changes in sitting vital signs (Study 148-231).

A36.5.3. Safety

There were no serious adverse events. One subject (age 77) discontinued with symptomatic hypotension after first receiving sildenafil. Three subjects on sildenafil and 1 subject on placebo dizziness that probably represented symptomatic hypotension.

A36.6. Summary

Sildenafil substantially decreased blood pressure for more than 6 hours and increased heart rate for about 2 hours when co-administered with glyceryl trinitrate, often to the point of being symptomatic.

A37. Study 148-232: A randomised, double-blind, placebo-controlled, crossover pilot study to investigate the effects of a single oral tablet dose of sildenafil (200mg) on visual function (electroretinogram, photostress, visual field and colour discrimination tests) in healthy male volunteers and patients with diabetic retinopathy.

A37.1. Source documents Study protocol NDA 20-895, vol 1.75; study report: NDA vol 1.75 and 4.4; electronic document: 45252576.pdf.

A37.2. Investigators Single-center study with 1 investigator in France.

A37.3. Study dates 12 November 1996 to 14 January 1997.

A37.4. Study design This study description was based upon the final study report, dated 22 August 1997.

A total of 8 normal volunteers and 8 subjects with diabetic retinopathy, age 40 to 65, were to be recruited.

Both normal volunteers and diabetic subjects participated in a 2-period, 2-arm crossover study. During the 2 periods 7 days apart, subjects received a single oral dose of placebo or sildenafil 200 mg in random order and underwent a battery of visual function tests consisting of visual acuity, photostress test, Farnsworth-Munsell 100-hue color discrimination test, and Amsler grid (tests for visual field defects in the central 10°). These assessments were made at baseline, and then 1, 2, 5, and 8 hours after dosing. Normal volunteers participated in a further 2 periods with the same double-blind treatments and underwent electroretinogram, Humphrey 30-2 visual field test, and assessment of intraocular pressure, at 1.25 and 5 hours after dosing.

Blood samples for assay of plasma levels of sildenafil and UK-103,320 were taken at baseline, 0.5, 1, 2, 3, 4, 5, and 8 hours after dosing.

Routine safety data were recorded.

A37.5. Results The study report only deals with results for normal volunteers.

A37.5.1. Conduct Eight normal subjects and 7 diabetic subjects were randomized and completed study. Diabetic subjects did not undergo ERG. All normal subjects received topical eye treatment following the ERG study. There were minor protocol deviations, but no subject was excluded from analyses.

A37.5.2. Pharmacokinetics Pharmacokinetic parameters following administration of sildenafil 200 mg are summarized in Table 128 below. Normal subjects and subjects with diabetes had similar findings. Times to peak were somewhat longer than in other studies.

Table 128. Pharmacokinetic parameters (Study 148-232).

	Sildenafil		UK-103,320	
	Normal	Diabetes	Normal	Diabetes
AUC (ng.h/mL)	2178	2155	1274	1176
C _{max} (ng/mL)	615	586	356	337
T _{max} (h)	2.2	3.4	2.3	3.6

A37.5.3. Pharmacodynamics Color discrimination error scores for normal subjects are shown in Table 129 below as a function of time after dosing. Figure 65 below shows the color distribution of errors in the 200-mg dose group at the time of peak plasma levels and highest error rate.

Only 3 normal subjects reported abnormalities on the Amsler grid visual field test, and 2 of those were on placebo. The photostress test showed no differences between treatment groups, but it could only have detected a 30% change. No subject on placebo

Table 129. Color discrimination error scores for normals (Study 148-232).

	Placebo			Sildenafil		
	1 h	2 h	5 h	1 h	2 h	5 h
Errors	78	77	89	100	129	97
Change from baseline	8	7	19	26	55	22

or sildenafil showed a change in visual acuity. There were no effects detected on intraocular pressure or in the Humphrey visual field test.

The photopic electroretinogram showed a treatment effect—50% reduction in the amplitude of the response to blue light statistically significant or nearly so at both 1.25 and 5 hours after dosing. Various components of the electroretinogram were delayed as well, typically by a few percent. The scotopic electroretinogram showed about a 30% reduction in amplitude at the 1.25- and 5-hour measurements of the response to orange light.

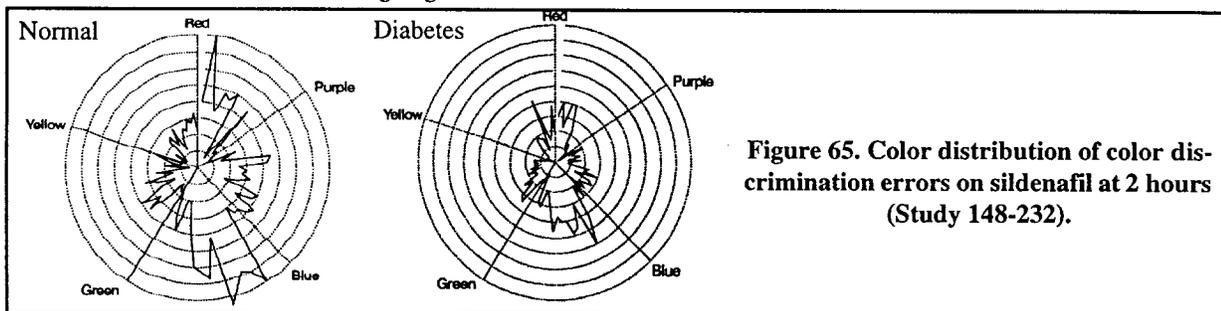


Figure 65. Color distribution of color discrimination errors on sildenafil at 2 hours (Study 148-232).

A37.5.4. Safety

There were no serious or treatment-related severe adverse reactions. Adverse events overall were more common on sildenafil, with headache and visual disturbances most notable on sildenafil among normal and diabetic subjects. Three normal and 4 diabetic subjects reported color-related visual disturbances, all shortly after exposure to sildenafil.

A37.6. Summary

Sildenafil was associated with aberrations in color vision manifest most clearly in the blue-green axis on color discrimination tests and also subjectively. Effects were also detectable by amplitude reduction and delays in the electroretinogram waveform in both the light- and dark-adapted states. Visual disturbances appear to have roughly tracked the time courses of plasma levels of sildenafil or its metabolite. None of the effects on vision appear to have been incapacitating. Subjects with diabetic retinopathy fared no worse than did normal volunteers.

Study 148-234: An open, randomised, placebo controlled, parallel group study to investigate the effects of multiple doses of erythromycin on the pharmacokinetics of a single 100mg dose of sildenafil.

NDA 20-895
Sildenafil for male impotence

A38. Study 148-234: An open, randomised, placebo controlled, parallel group study to investigate the effects of multiple doses of erythromycin on the pharmacokinetics of a single 100mg dose of sildenafil.

A38.1. Source documents Study protocol NDA 20-895, vol 4.3; study report: NDA vol 4.3; electronic document: 46504995.pdf.

A38.2. Investigators

A38.3. Study dates 24 February 1997 to 20 May 1997.

A38.4. Study design This study description was based upon the final study report, dated 19 November 1997.

A38.4.1. Objectives

The objectives were

- To investigate the effects of multiple doses of erythromycin (500 mg bid) on the pharmacokinetics of a single 100-mg dose of sildenafil.
- To investigate the safety and toleration of sildenafil co-administered with erythromycin.

A38.4.2. Formulation

Drug supplies were 250-mg erythromycin tablets, lot 87033VA, placebo lot 3039-124A, and 100-mg sildenafil tablets, lot 4469-115.

A38.4.3. Population

A total of 24 healthy male volunteers, age 18 to 45, were recruited.

A38.4.4. Procedures

This was an open, randomized, placebo controlled, parallel controlled study. On day 1, all subjects received a single dose of sildenafil 100 mg. Subjects were then allocated to either one of 2 treatment groups. On days 2 to 6, one group of 12 subjects received erythromycin 500 mg twice daily and the other group of 12 subjects was to receive placebo twice daily. On day 6 all subjects received a single dose of sildenafil 100 mg one hour after dosing with erythromycin. On days 1 and 6, blood samples for the measurement of sildenafil and its metabolite were collected at the following time points: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose.

A38.4.5. Assay

A38.4.6. Analysis

Pharmacokinetic parameters were calculated using standard non-compartmental techniques. The difference between the mean values on day 1 and day 6 was estimated for each treatment group, together with the associated standard error and 95% confidence interval for the difference. For comparisons of AUC and C_{MAX}, the linearized ratio and confidence intervals were also presented.

A38.4.7. Safety

Routine safety data were recorded.

A38.5. Results

A38.5.1. Conduct

Twenty-six subjects were randomized and all but one in each group completed all study phases. Protocol violations appear to have been minor.

A38.5.2. Pharmacokinetics

Mean plasma concentration time profiles for sildenafil and its metabolite for day 1 and 6 for both the placebo and erythromycin treated groups are shown in Figure 66 below and the corresponding parameters are summarized in Table 130 below.

The results show that for sildenafil, coadministration with erythromycin both increased the AUC and C_{max} of sildenafil by 2.6- and 2.1-fold, respectively. This

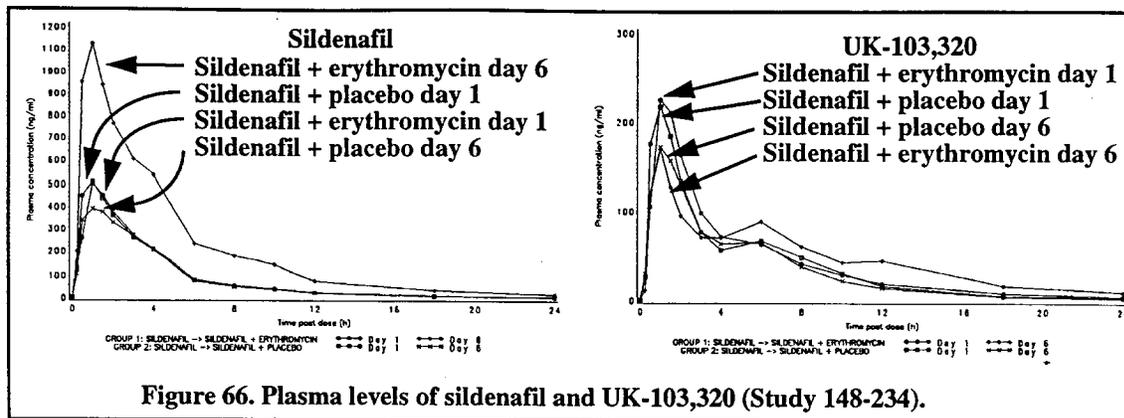


Figure 66. Plasma levels of sildenafil and UK-103,320 (Study 148-234).

Table 130. Pharmacokinetic parameters (Study 148-234).

	Sildenafil				UK-103,320			
	Placebo		Erythromycin		Placebo		Erythromycin	
	Day 1 ^a	Day 6	Day 1	Day 6	Day 1	Day 6	Day 1	Day 6
AUC (ng.h/mL)	1893	1732	1904	4911	867	769	905	1099
AUC _τ (ng.h/mL)	1879	1718	1889	4832	853	757	884	1031
C _{max} (ng/mL)	639	512	596	1245	277	227	270	169
T _{max} (h)	1.0	1.2	1.1	0.8	0.9	1.2	1.1	0.9
k _{el} (h ⁻¹)	0.21	0.20	0.20	0.17	0.18	0.19	0.16	0.13
t _{1/2} (h)	3.3	3.5	3.5	4.1	3.9	3.6	4.2	5.3

a. Both groups received sildenafil alone on day 1, and then sildenafil plus erythromycin or placebo on day 6.

increase in exposure most probably did not result from inhibiting the elimination pathway for sildenafil, since the elimination rate constant was not affected by erythromycin.

As for the effect of erythromycin on the levels of the metabolite UK-103,320, the ratio of geometric AUC means was 1.2 while the ratio of geometric C_{max} was 0.6. The results also show that multiple dosing of erythromycin increased the half-life of the metabolite by 1 hour (from 4.2 to 5.3 hours). This increase in t_{1/2} was found to be statistically significant.

A38.5.3. Safety

There were no serious or severe adverse events reported. Headache, vasodilation, abnormal vision, and penile erections were reported with both treatments, at roughly the same rate.

A38.6. Summary

These findings strongly suggest that erythromycin inhibits CYP3A4 found in the gastrointestinal tract, thereby affecting pre-systemic metabolism of sildenafil. The magnitude of increase in plasma levels of sildenafil suggests that patients who are on known inhibitors of CYP3A4 should be started on the lowest possible dose—25 mg—and titrated up as needed, although the safety results of this study do not indicate this is a major safety concern.

A39. Study 148-301: An open single intravenous dose study of the haemodynamic effects of UK-92,480 (sildenafil) in patients with stable ischaemic heart disease.

A39.1. Source documents Study protocol NDA 20-895, vol 1.77; study report: NDA vol 1.77; electronic document: 46822388.pdf.

A39.2. Investigators Single-center study with 1 investigator in the United Kingdom.

A39.3. Study dates 6 April 1993 to 7 September 1993.

A39.4. Study design This study description was based upon the final study report, dated 24 March 1997.

A total of 10 subjects with stable, uncomplicated ischemic heart disease, age 18 to 70, were to be recruited.

Subjects were to have vasoactive drugs withheld 48 hours prior to right heart catheterization. Subjects underwent a baseline 4-minute exercise test and then had hemodynamic measurements made beginning after 20 or more minutes of rest. Sildenafil was administered by intravenous infusion to provide 10 mg over the first 30 minutes, 10 mg over the next 15 minutes, and then 20 mg over the final 15 minutes (total of 40 mg over 1 hour). Hemodynamic measurements were made in the 3 minutes prior to the end of four 15-minute sampling periods. Assessments to be made included systemic arterial pressure, pulmonary artery wedge pressure, pulmonary artery pressure, right atrial pressure, heart rate, cardiac volume, stroke volume, systemic vascular resistance, pulmonary vascular resistance, and left and right ventricular work indices.

Blood samples for assay of plasma levels of sildenafil were taken at baseline and at the end of each 15-minute period of infusion.

Routine safety data were recorded.

A39.5. Results

A39.5.1. Conduct Eight subjects were randomized and completed study. Some of the derived parameters were not reported.

A39.5.2. Pharmacokinetics Mean plasma levels by 15-minute period were 153 to 174, 217 to 278, 432 to 708, and 950 to 2023 ng/mL, respectively.

A39.5.3. Pharmacodynamics Selected hemodynamic data (mean±SD) are shown in Table 131 below. In general, pressures were somewhat lower following sildenafil than after placebo.

Table 131. Hemodynamic data at highest dose (Study 148-301).

	At rest		After exercise	
	Baseline	Sildenafil	Baseline	Sildenafil
PAWP (mmHg)	11±4.8	7.8±4.7	36±13.7	28±15.3
Mean PAP (mmHg)	18±3.9	13±4.1	39±12.9	32±13.2
Mean RAP (mmHg)	5.7±3.7	4.1±3.7	—	—
SBP (mmHg)	155±17	143±17	200±37	188±30
DBP (mmHg)	74±8.3	63±15	85±9.7	80±9.4
CO (L/min)	6.6±1.6	5.2±0.4	12±2.4	10±3.5
Heart rate (bpm)	64±9.8	70±14	102±12	99±20

A39.5.4. Safety One subject died after emergency CABG on day 12 after dosing. There were no other noteworthy findings.

A39.6. Summary

At these doses, intravenous sildenafil produced modest changes in pulmonary and systemic blood pressures. The dose-response relationship and the time course of these effects were not well-characterized by the study.

Study 148-350: A double blind, randomised, placebo controlled, two way crossover pilot study to investigate the efficacy and safety of UK-92,480 (sildenafil, 25mg tid for 7 days) in patients with impotence.

NDA 20-895
Sildenafil for male impotence

A40. Study 148-350: A double blind, randomised, placebo controlled, two way crossover pilot study to investigate the efficacy and safety of UK-92,480 (sildenafil, 25mg tid for 7 days) in patients with impotence.

- A40.1. Source documents** Study protocol NDA 20-895, vol 1.78; study report: NDA vol 1.787; electronic document: 47081406.pdf.
- A40.2. Investigators** Single-center study with 1 investigator in the United Kingdom.
- A40.3. Study dates** 28 July 1993 to 15 November 1993.
- A40.4. Study design** This study description was based upon the final study report, dated 8 August 1997.

A total of 16 subjects with a 6-month history of erectile dysfunction of no known neurological or vascular cause, age 18 to 70, were to be recruited.

For two study periods 7 days apart, subjects received in random order placebo or sildenafil 25 mg tid for 7 days. The last dose on the evening of 7th day was administered in the clinic where penile plethysmography was performed for 10 hours in the setting of visual sexual stimulation.

During at-home dosing, subjects maintained a diary of erections and erections associated with sexual stimulation.

Routine safety data were recorded.

A40.5. Results

A40.5.1. Conduct

Sixteen subjects were randomized and 15 completed both phases of the study. Minor protocol violations were described, but the only subject excluded from the plethysmography assessment was one who did not participate in the second crossover phase.

A40.5.2. Pharmacodynamics

Penile plethysmography data (Rigiscan) obtained during presentation of sexual stimulation are shown in Table 132 below. There was no treatment effect during the succeeding 8 hours of monitoring.

Table 132. Penile plethysmography (Study 148-350).

	Placebo	Sildenafil	P
Duration >60% (base; min)	12	49	0.005
Duration >60% (tip; min)	7.4	36	0.002
Duration >80% (base; min)	3.5	15	0.002
Duration >80% (tip; min)	1.2	10	0.0006

Diary data showed a nominally statistically significant increase in erections on sildenafil, but interpretation is complicated by apparent treatment period effects.

A40.5.3. Safety

One subject discontinued from dosing on active treatment because of dyspepsia, considered treatment-related. Adverse events were more commonly reported on sildenafil, the most common of which were headaches and myalgia involving the back and legs.

A40.6. Summary

The Rigiscan and diary data are consistent with a clinically significant improvement of erectile function in subjects receiving sildenafil 25 mg tid. The trial design does not permit any assessment of the time course of effects after a dose or with repeated dosing.

A41. Study 148-351: A double blind, randomised, placebo controlled, four way crossover study followed by a double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of UK-92,480 (sildenafil) in patients with erectile dysfunction with no established organic cause.

- A41.1. Source documents** Study protocol NDA 20-895, vol 1.79; study report: NDA vol 1.79; electronic document: 47081294.pdf.
- A41.2. Investigators** Single-center study with 1 investigator in the United Kingdom.
- A41.3. Study dates** 24 February 1994 to 30 May 1994.
- A41.4. Study design** This study description was based upon the final study report, dated 15 July 1997.

A total of 12 subjects with a 6-month history of erectile dysfunction of no known neurological¹ cause, age 18 to 70, were to be recruited.

The study consisted of two parts. In the first part, subjects received, in random order, single doses of placebo and sildenafil 10, 25, and 50 mg on separate study days 3 days apart. These subjects underwent penile plethysmography accompanied by visual sexual stimulation. Blood samples for plasma sildenafil and UK-103,320 were obtained at the end of a 2.5-hour Rigiscan evaluation. In the second part, subjects received, in random order, placebo and sildenafil 25 mg per day for 7 days in phases separated by 7 days. Subjects maintained a diary during these two 1-week periods.

Routine safety data were recorded.

A41.5. Results

A41.5.1. Conduct Twelve subjects were randomized and all completed both parts of the study. All subjects reported spontaneous erections. Minor protocol violations were described, but no subject was excluded from analyses.

A41.5.2. Pharmacokinetics Mean plasma levels at 2.5 hours after dosing were 26 ng/mL after 10 mg, 62 ng/mL after 25 mg, and 122 ng/mL after 50 mg. Corresponding mean levels of UK-103,320 were about 40% of the parent compound.

A41.5.3. Pharmacodynamics Penile plethysmography data (Rigiscan) obtained during presentation of sexual stimulation are shown in Table 133 below. Plasma levels of sildenafil or its metabolite correlated strongly with Rigiscan data, but accounted for a small fraction of the observed variance. In all subjects with plasma concentrations >100 ng/mL, the duration of >60% rigidity exceeded 30 minutes.

Table 133. Penile plethysmography (Study 148-351).

	Placebo	Sildenafil		
		10 mg	25 mg	50 mg
Duration >60% (base; min)	3.2	26	24	32
Duration >60% (tip; min)	2.9	19	26	27
Duration >80% (base; min)	1.4	3.5	7.7	11
Duration >80% (tip; min)	1.1	4.6	6.7	7.4

Diary data showed a statistically significant increase in erections on sildenafil.

A41.5.4. Safety Minor adverse events were reported with no clear relationship to treatment.

¹The intent was clearly to enroll subjects with psychogenic erectile dysfunction, but the exclusion criteria do not appear to encompass erectile dysfunction of vascular etiology. All subjects enrolled had erectile dysfunction attributed to psychogenic etiology.

Study 148-351: A double blind, randomised, placebo controlled, four way crossover study followed by a double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of UK-92,480

*NDA 20-895
Sildenafil for male impotence*

A41.6. Summary

This was an early demonstration of effects of sildenafil on erectile function in subjects with no established organic cause.

Study 148-353: A randomised, double-blind, placebo controlled, parallel-group, multicentre, dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered once daily for 28 days to patients with erectile dysfunction.

NDA 20-895
Sildenafil for male impotence

A42. Study 148-353: A randomised, double-blind, placebo controlled, parallel-group, multicentre, dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered once daily for 28 days to patients with erectile dysfunction.

A42.1. Source documents Study protocol NDA 20-895, vol 1.116; study report: NDA vol 1.116; electronic document: 47098656.pdf.

A42.2. Investigators Multi-center study with 36 investigators in France, Sweden, and United Kingdom.

A42.3. Study dates 5 September 1994 to 25 July 1995.

A42.4. Study design This study description was based upon the amended protocol dated 17 June 1994. There is no mention of amendments.

Drug supplies are shown in Table 134 below.

Table 134. Drug supplies (Study 148-353).

	Lot		Lot
Placebo	3039-100	Sildenafil 5 mg	3039-131 3039-050
		Sildenafil 25 mg	3039-133 3039-135

The intent was to randomize 300 male subjects age >18, with erectile dysfunction of >3 months' duration, and in a heterosexual relationship. Subjects were excluded for (1) advanced vascular or neurological erectile dysfunction, (2) regular use of nitrates, anticoagulants, major tranquilizers, estrogens, or antiandrogens, (3) elevated prolactin or low testosterone, (4) major hematologic, renal, or hepatic disease, (5) history of stroke, bleeding disorder, or active peptic ulcer disease, (6) postural hypotension or blood pressure outside 90/50 to 170/110 mmHg, (7) experimental drug use within 3 months, (8) alcohol abuse, (9) blood donation within 1 month, (10) HBsAg positivity, (11) significant abnormalities at screening, and (12) inadequate compliance during screening.

At the end of a 2-week treatment-free run-in period during which baseline sexual performance data were collected, subjects were randomized to placebo or sildenafil 10, 25, or 50 mg and followed for 4 weeks. Subjects were instructed to take study drug once per day. Subjects completed an event log noting time of study drug administration and subsequent sexual activity. Subjects completing study without serious adverse events were eligible to participate in a 52-week open-label study.

The primary efficacy assessment was at week 4. The primary end points were (1) the proportion of subjects reporting an improvement in erections, (2) the proportion of subjects interested in continuing treatment, and (3) weekly erection count.

Routine safety data were recorded.

A42.5. Results

A42.5.1. Conduct Four hundred and four subjects were screened, 351 were randomized, and 317 (90%) completed study.

Demographics of the 4 treatment groups are shown in Table 135 below.

Protocol violations are described in Table 136 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 135. Demographics (Study 148-353).

		Placebo N=95	Sildenafil		
			10 mg N=90	25 mg N=85	50 mg N=81
Race (%)	White	91	90	94	94
	Black	6.3	5.6	3.5	1.2
	Other	3.2	4.4	2.4	4.9
Age	Mean	53	52	53	52
	Range	26-70	28-70	24-70	26-69
Etiology (%)	Psychogenic	54	59	61	59
	Mixed	46	41	39	41
Duration (y)	Mean	4.3	4.7	4.5	4.5
	Range	0.3-40	0.4-30	0.3-30	0.3-23
Med hx (%)	Hypertension	14	8.9	18	12
	Diabetes	1.1	3.3	3.5	1.2
	Prostatectomy	2.1	3.3	2.4	2.5

Table 136. Protocol violations (Study 148-353).

At randomization		On treatment	
	n		n
Screen phase compliance low	24	Compliance	24
Appropriate consent lacking	7	No efficacy data	12
No erections during screening	3		
Organic erectile dysfunction	3		
Concomitant meds	1		
Total ^a	38	Total	36

a. Some subjects had more than one violation.

A42.5.2. Effectiveness

Affirmative responses to global questions are summarized in Table 137 below. The mean number of erections per week per subject varied monotonically from 1.8 in placebo (same as overall mean baseline rate) to 3.8 on 50 mg.

Table 137. ITT analyses of global effectiveness data (Study 148-353).

	Placebo N=95		Sildenafil						P
			10 mg N=90		25 mg N=85		50 mg N=81		
	n	%	n	%	n	%	n	%	
Treatment has improved erections	91	39	84	64	82	79	76	88	<0.0001
Would use this treatment again	87	51	82	78	78	84	75	91	<0.0001

Secondary end points from the other Sexual Function Questionnaire (SFQ) questions are described in Table 138 below (sponsor's analyses only). There is a fairly consistent pattern, with significant treatment effects generally confined to effects pertaining to erectile function and then less compelling and less consistent effects in areas like satisfaction with intercourse or satisfaction more generally.

Table 138. ITT analyses of non-primary SFQ questions at week 4 (Study 148-353)^a.

Domain	Question	Base-line	Sildenafil								p
			Placebo N=95		25 mg N=90		50 mg N=85		100 mg N=81		
			n	Q	n	Q	n	Q	n	Q	
Erectile function	Waking erections	2.7	94	2.7	90	2.9	85	3.0	78	3.2	0.007
	Frequency of stimulated erections	2.4	94	2.7	90	2.9	85	3.1	78	3.4	0.003
	Firmness of erections	2.0	91	2.4	90	2.9	80	3.0	74	3.3	<0.0001
	Duration of erections	1.5	91	2.1	90	2.6	80	2.8	75	3.2	<0.0001
Intercourse satisfaction	Attempted intercourse	2.9	83	3.1	72	3.6	69	3.8	63	4.3	0.08
	Satisfaction of intercourse	1.3	69	2.1	66	2.5	60	3.0	49	4.0	0.004
	Enjoyment of intercourse	3.4	94	2.1	88	2.8	85	3.0	76	3.2	<0.0001
Orgasmic function	Frequency of ejaculation	3.5	94	3.6	89	4.0	85	4.0	78	4.5	0.0009
Sexual desire	Frequency of desire	3.0	94	3.2	90	3.2	85	3.4	78	3.6	0.03
	Rating of desire	2.8	94	3.0	90	3.1	85	3.1	78	3.3	0.2
Overall satisfaction	Satisfaction with sex life	2.2	93	2.4	88	2.9	85	3.1	77	3.5	<0.0001
	Self confidence	2.9	76	3.0	67	3.2	70	3.1	60	3.4	0.09
	Satisfaction with relationship	3.2	76	3.2	66	3.7	70	3.6	60	3.6	0.05
	Enjoyment of life	3.5	76	3.5	67	3.6	70	3.7	60	3.8	0.07

a. Sponsor's analyses.

About 66% of partners responded on the partner questionnaire. There strongly dose-related improvements in partners' assessments of quality of erections and their own sex lives.

A42.5.3. Safety

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

A42.6. Summary

All subjects had erectile dysfunction wholly or partly of psychogenic origin. The placebo response rate (as assessed by subjects' assertion that treatment had improved erections) was predictably high. Nonetheless, substantial dose-related effects were demonstrated, by sexual function questionnaire and erections per week.

A43. Study 148-354A: An open, non-comparative study to assess the efficacy and safety of UK-92,480 (sildenafil) taken over a 52-week period by patients with erectile dysfunction.

- A43.1. Source documents** Study protocol NDA 20-895, vol 1.132; study report: NDA vol 1.132; electronic document: 46006894.pdf.
- A43.2. Investigators** Multi-center study with 36 investigators in United Kingdom, France, and Sweden.
- A43.3. Study dates** 20 December 1994 to 3 September 1996.
- A43.4. Study design** This study description was based upon the amended protocol dated 7 April 1995. There were 2 minor amendments.

Drug supplies are shown in Table 139 below.

Table 139. Drug supplies (Study 148-354A).

	Lot		Lot
Sildenafil 10 mg	3039-132	Sildenafil 25 mg	3039-134A
	3039-132A		3509-044
	3509-042		3509-051
			3509-078
			3509-080
			3509-081

Subjects were all previous participants in studies 148-350¹, 148-351², 148-353³, or 148-355⁴. Subjects must have completed the blinded study without a serious adverse event possibly related to study drug.

Visits were scheduled at 4, 8, 16, 24, 36, and 52 weeks. Subjects began on 25 mg, but could have their doses adjusted between 10 and 100 mg. The primary end point was whether subjects were interested in continuing treatment, subjects' assessments of erections, and the proportion of responders by dose. Subjects also kept an event log and completed a sexual function questionnaire.

Routine safety data were collected.

A43.5. Results

A43.5.1. Conduct

Three hundred and eight subjects entered long-term open-label study, and 269 (87%) completed study.

The mean age was 54 years. Ninety-three percent were Caucasian. The mean duration of erectile dysfunction was 4 years. Etiology of erectile dysfunction was organic in 0.7%, psychogenic in 57%, and mixed in 42%.

- ¹ A double-blind, randomized, placebo-controlled two-way crossover pilot study to investigate the efficacy and safety of UK-92,480 (25 mg tid for 7 days) in patients with impotence.
- ² A double-blind, randomized, placebo-controlled, 4-way crossover study followed by a double-blind, randomized, placebo-controlled, two-way crossover study to investigate the effect of single doses of UK-92,480 in patients with erectile dysfunction with no established organic cause.
- ³ Study 148-353: A randomised, double-blind, placebo controlled, parallel-group, multicentre, dose-response study to assess the efficacy and safety of sildenafil (UK-92,480) administered once daily for 28 days to patients with erectile dysfunction. on page 186.
- ⁴ Study 148-355: A double blind, randomised, placebo controlled, two way crossover study to investigate the efficacy of single doses of sildenafil (UK-92,480) (taken when required over a 28 day period) in patients with erectile dysfunction with no established organic cause. on page 191.

A variety of protocol violations included more than one dose per day (38), participation for more than 52 weeks (24), and use of forbidden concomitant medications (32).

Thirteen percent of subjects discontinued. Reasons for discontinuation included lack of effectiveness (3%, mostly titrated to the highest allowed dose) and adverse events or laboratory abnormalities.

Exposure is characterized in Figure 67 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.

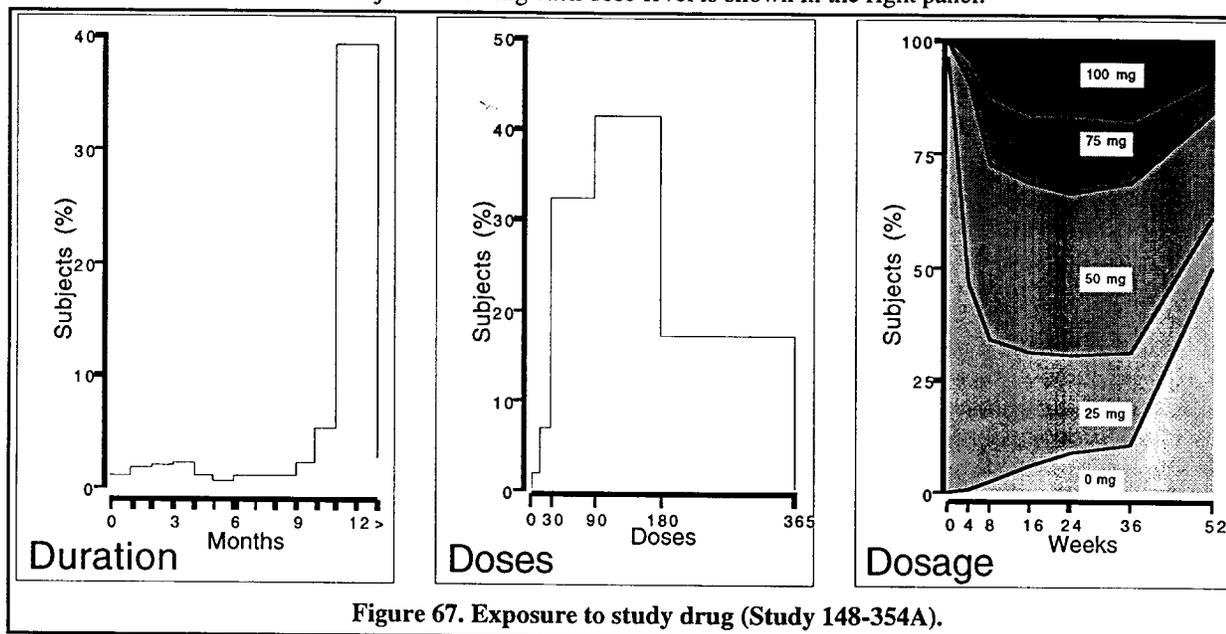


Figure 67. Exposure to study drug (Study 148-354A).

A43.5.2. Effectiveness

By the sponsor's analyses, the proportion of subjects indicating improvement in erections was 88% and the proportion indicating an interest in continuing treatment was 90%. There were significant improvements from baseline for each of 7 items in the sexual function questionnaire. The reviewers performed no analyses of these data.

A43.5.3. Safety

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

A43.5.4. Long-term

Documentation is incomplete. One hundred and thirty-two subjects entered the 52-week, long-term, open-label extension to Study 148-354A. As of the cut-off date of 3 February 1997, 0 subjects had completed, and 0 subjects had withdrawn. One subject on β -blocker reported a syncopal episode after a hot bath. Two subjects reported visual disturbances. Common adverse events were headache (5%), vasodilation/flushing (7%), and dyspepsia (5%).

A43.6. Summary

The study population's erectile dysfunction was wholly or partly psychogenic in etiology. The absence of a control group makes it difficult to assess effectiveness. Most subjects gravitated to the 50-mg dose, not the highest dose available.