

Center for Drug Evaluation and Research

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Appendix A10, page 104 through Appendix A13.6, page 125

Study 148-102: A double-blind, randomized, placebo-controlled, parallel group, fixed-dose, multicenter study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction.

NDA 20-895
Sildenafil for male impotence

A10. Study 148-102: A double-blind, randomized, placebo-controlled, parallel group, fixed-dose, multicenter study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction.

A10.1. Source documents Study protocol IND vol 15.1; study report: NDA vol 1.91-1.94; electronic document: 47099527.pdf; SAS datasets.

A10.2. Investigators Multi-center study with 23 investigators in the United States.

A10.3. Study dates 30 November 1995 to 30 October 1996.

A10.4. Study design This study description was based upon the amended protocol dated 4 April 1996. On 25 January 1996, the primary end point was changed, upon advice by FDA, to be sexual performance-related (questionnaire) rather than erectile function (questionnaire). The same amendment called for the primary analysis to be based upon an "ITT" population with at least one efficacy assessment post-baseline.

Drug supplies are shown in Table 73 below.

Table 73. Drug supplies (Study 148-102).

	Lot		Lot
Placebo 25 mg	ED-S-362-995 ED-S-363-995	Sildenafil 25 mg	ED-S-355-995
Placebo 50 mg	ED-S-350-995 ED-S-351-995 ED-S-352-995 ED-S-353-995	Sildenafil 50 mg	ED-S-356-995 ED-S-358-995

The intent was to randomize 500 male subjects age >18, with erectile dysfunction¹ 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 to placebo or sildenafil 25, 50, or 100 mg and followed for 24 weeks. A 2:1 placebo:active randomization was implemented to compensate for the expected differences in the rate of withdrawal for lack of efficacy. 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 4, 8, 12, 16, and 24, 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.

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

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.

Plasma samples were drawn for determination of parent compound and metabolite UK-103,320 at weeks 2, 4, 8, 12, and 24, a random, but recorded, time after the last dose.

The study was originally sized to achieve 80% power at $\alpha=0.05$ to detect a 70% improvement in erections on study drug compared with a 50% improvement on placebo. The study was not resized when the end point was changed. 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.

A10.5. Results

A10.5.1. Conduct

Six hundred and four subjects were screened, 532 were randomized, and 465 (87%) completed study. Individual sites enrolled 3 to 40 subjects.

Demographics of the 4 treatment groups are shown in Table 74 below. About half of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 9% had used non-drug treatments.

Table 74. Demographics (Study 148-102).

		Placebo N=216	Sildenafil		
			25 mg N=102	50 mg N=107	100 mg N=107
Race (%)	White	85	88	91	91
	Black	9.7	5.9	7.5	6.5
	Other	5.1	7.8	1.9	2.8
Age	Mean	57	58	57	59
	Range	20-79	24-79	29-81	25-87
Etiology (%)	Organic	77	76	80	77
	Psychogenic	10	7	8	11
	Mixed	13	17	11	12
Duration (y)	Mean	3.2	2.9	3.2	3.5
	Range	0.4-20	0.5-11	0.5-14	0.1-16
Med hx (%)	Hypertension	31	35	34	30
	Diabetes	16	19	12	9
	Prostatectomy	15	18	20	17
	Depression	6.5	6.9	5.6	8.4
	IHD	9.7	6.9	13	13

Protocol violations are described in Table 75 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 75. Protocol violations (Study 148-102).

At randomization		On treatment	
	n		n
Prohibited meds	30	>1 dose/day	56
Baseline lab abn	25	Blind broken for AE	9
Peyronie's disease or anatomic defect	23		
Psychiatric disorder	19		
Ethanol or drug abuse	13		
Confounding condition/treatment	9		
Poorly controlled hypertension	4		
Use of other experimental drug	1		
Sexually transmitted disease	1		
Erectile dysfunction <6 months	1		
Total ^a	114	Total	64

a. Some subjects had more than one violation.

The disposition of subjects in the trial is shown in Figure 32 below, which shows the placebo group in the left panel and all active treatment groups combined in the right panel. Most subjects remained in study for more than 24 weeks, but some "completed" several weeks early. As the sponsor predicted, fewer subjects on active treatment withdrew for lack of efficacy (or withdrew consent).

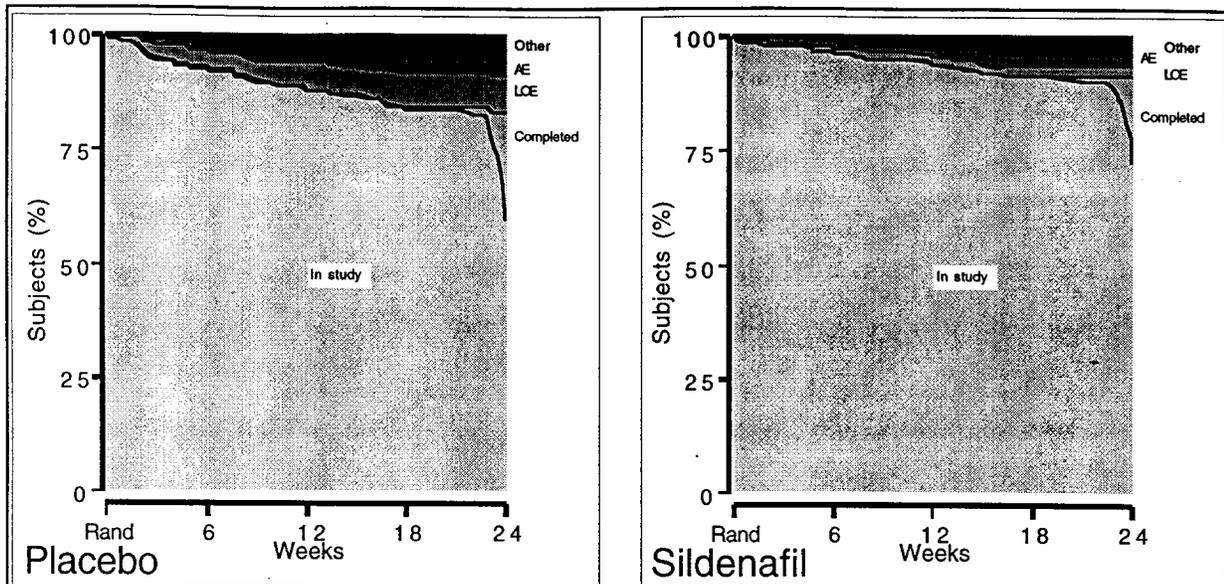


Figure 32. Disposition of subjects (Study 148-102).

The reviewers counted all subjects as “in study” until they reach a state in an all-inclusive set of mutually exclusive final states. In this particular case, the band labeled “LOE” (lack of efficacy) includes subjects who withdrew consent, the band labeled “AE” (adverse event) includes subjects withdrawn for laboratory abnormalities, and the “Other” band includes subjects withdrawn for protocol violations and subjects lost to follow-up.

A10.5.2. 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 attempts², 1 for never or rarely successful, etc., up to 5 for always or almost always successful. The sponsor’s analyses were LOCF, which tends to make placebo, which had a higher withdrawal rate, better than it otherwise would be. Results are summarized in Table 76 below.

Table 76. ITT analyses of IIEF questions 3 and 4 (Study 148-102).

		Placebo N=216		Sildenafil						P ^a
		25 mg N=102		50 mg N=107		100 mg N=107				
		n	Q ^b	n	Q	n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	2.0 ^c	—	—	—	—	—	—	
	Week 12	190	2.3	95	3.3	100	3.7	96	4.0	<0.0001
	Week 24	199	2.2	96	3.2	105	3.5	100	4.0	<0.0001
How often were you able to maintain your erection after penetration?	Baseline	—	1.6	—	—	—	—	—	—	
	Week 12	189	2.2	95	3.2	100	3.5	96	3.9	<0.0001
	Week 24	199	2.1	96	3.1	105	3.5	101	3.9	<0.0001

- a. P-value for non-zero slope to dose-response.
- b. Mean score.
- c. Pooled baseline value for all subjects.

Secondary end points from the other IIEF questions are described in Table 77 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.

except for those pertaining to sexual desire, for which there appeared to be no treatment effect at week 12. Generally similar findings were obtained at week 24, but a small treatment effect on sexual desire was also nominally statistically significant at week 24.

Table 77. ITT analyses of non-primary IIEF questions at week 12 (Study 148-102)^a.

Domain	Question	Base-line	Placebo N=216		Sildenafil						p ^b
					25 mg N=102		50 mg N=107		100 mg N=107		
			n	Q	n	Q	n	Q	n	Q	
Erectile function	Able to get erection	2.5	189	2.9	95	3.8	100	4.0	97	4.4	<0.0001
	Erections hard enough	2.1	190	2.1	95	3.3	99	3.8	97	4.0	<0.0001
	Erection maintained to completion	1.5	190	2.1	95	3.2	100	3.6	97	3.9	<0.0001
	Confidence in erection	1.6	190	2.1	95	2.7	98	3.3	96	3.4	<0.0001
Intercourse satisfaction	Attempted intercourse	1.9	191	2.7	95	3.1	100	3.0	97	3.6	<0.0001
	Satisfaction of intercourse	1.8	191	2.3	94	3.4	100	3.7	97	3.9	<0.0001
	Enjoyment of intercourse	1.8	191	2.3	94	3.0	100	3.6	97	3.8	<0.0001
Orgasmic function	Frequency of ejaculation	3.1	189	3.2	93	4.0	97	4.2	97	4.3	<0.0001
	Frequency of orgasm	3.0	190	3.2	94	3.5	100	4.2	97	4.1	<0.0001
Sexual desire	Frequency of desire	3.5	190	3.3	95	3.3	100	3.5	97	3.6	0.2
	Rating of desire	3.2	190	3.2	95	3.3	100	3.4	97	3.3	0.2
Overall satisfaction	Satisfaction with sex life	1.9	190	2.4	95	3.1	100	3.4	97	3.6	<0.0001
	Satisfaction with relationship	2.7	187	3.1	94	3.7	100	3.8	95	4.1	<0.0001

a. Sponsor's analyses.

b. P-value for non-zero slope to dose-response.

About 25% of placebo group partners and 33% of active group partners responded on the partner questionnaire, which is perhaps as telling as the observed statistically significant treatment effects, at 12 and 24 weeks, on questions to rate the partner's erections and satisfaction of sexual intercourse.

The global assessment by subjects whether treatment improved their erections, the original primary end point, was answered in the affirmative at week 12 by 27% on placebo, 58% on 25 mg, 74% on 50 mg, and 81% on 100 mg. Results were similar at 24 weeks.

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. Table 78 below therefore combines results of the sponsor's and the reviewers' analyses.

The only quality of life component (out of 11) with a statistically significant treatment effect (by the sponsor's analyses), at both week 12 and week 24, was impact of erectile dysfunction on quality of life.

The reviewers analyzed the proportion of subjects improving, staying the same, or worsening, on the primary effectiveness questions, by treatment group, at week 24, as shown in Table 79 below.

The reviewers also carried out an analysis of the primary end point on sub-groups defined by etiology of erectile dysfunction, duration of erectile dysfunction, history of nocturnal erections, history of prior treatment for erectile dysfunction, and history of

Table 78. Successful intercourse by event logs (Study 148-102).

	Sponsor (12 weeks)				Reviewers (24 weeks)			
	Placebo N=216	Sildenafil			Placebo N=216	Sildenafil		
		25 mg N=102	50 mg N=107	100 mg N=107		25 mg N=102	50 mg N=107	100 mg N=107
Attempts								
Total	—	—	—	—	14004	7023	7795	7055
Per subject mean	—	—	—	—	65	69	73	66
Successes								
Total	—	—	—	—	3388	2701	3994	3627*
Per subject mean	—	—	—	—	16	26	37	34
Success by attempts (%)	22	39	54	56	24	38	51	51
Success by subjects (%)								
During run-in	—	—	—	—	43	33	47	48
During DB treatment	—	—	—	—	69	86	89	92

Table 79. ITT shift analyses of IIEF questions 3 and 4 at week 24 (Study 148-102).

		Placebo N=198	Sildenafil		
			25 mg N=96	50 mg N=107	100 mg N=107
How often were you able to penetrate your partner?	Decr (%)	28	15	8	8
	Same (%)	40	40	35	22
	Incr (%)	31	46	57	71
How often were you able to maintain your erection after penetration?	Decr (%)	22	14	7	9
	Same (%)	45	31	27	21
	Incr (%)	33	55	66	72

diabetes mellitus. The results of comparisons of the slope of the dose-response curves (change in score per g) are summarized in Table 80 below. The results are consistent with there being similar treatment effects regardless of classification of etiology, presence or absence of nocturnal erections, previous use of drugs or devices for treatment of erectile dysfunction, or duration of erectile dysfunction. Of the factors evaluated, only subjects with a history of diabetes mellitus appeared to have a reduced treatment effect, as indicated by smaller estimates of the slope in subjects with diabetes, statistical significant treatment*diabetes interaction, and the lack of nominal statistical significance for the slope.

Table 80. Sub-group analyses of IIEF questions 3 and 4^a (Study 148-102).

	N	How often were you able to penetrate your partner?				How often were you able to maintain your erection after penetration?			
		Factors ^b	Intcpt	Slope	P ^c	Factors	Intcpt	Slope	P
Etiology		Baseline				Baseline			
Organic	411	Age	0.2±0.1	16±2	0.0001		0.4±0.1	15±2	0.0001
Psychogenic	50	Etiology	0.2±0.2	23±5	0.0001		0.1±0.2	28±5	0.0001
Mixed	70		0.7±0.3	19±6	0.003		1.1±0.3	16±5	0.005
Nocturnal erections		Baseline				Baseline			
Yes	308	Noct	0.5±0.1	18±2	0.0001	Noct	0.7±0.1	18±2	0.0001
No	175		0.0±0.1	16±3	0.0001		0.1±0.2	15±3	0.0001
Unknown	48		0.2±0.4	17±6	0.01		0.7±0.4	12±7	0.09
Duration		Baseline				Baseline			
<3 years	325		0.1±0.1	19±2	0.0001	Age	0.5±0.1	17±2	0.0001
>3 years	206		0.5±0.1	13±3	0.0001		0.5±0.1	17±3	0.0001
Previous treatment		Baseline				Baseline			
Yes	284		0.4±0.1	16±3	0.0001	Age	0.6±0.1	15±3	0.0001
No	247		0.1±0.1	17±2	0.0001		0.3±0.1	18±3	0.0001
Diabetes mellitus		Baseline				Baseline			
Yes	72	Tx*diabetes	0.4±0.2	5±5	0.29	Age	0.5±0.2	8±5	0.11
No	459		0.3±0.1	18±2	0.0001	Tx*diabetes	0.5±0.1	17±2	0.0001

a. Reviewers' LOCF analyses; slope of dose-response (change in score per g)

b. Statistically significant effects ($P < 0.05$) by ANCOVA from among baseline score, age classified as <55 or >55, sub-grouping (etiology, etc.), treatment by age (Tx*age) interaction, or treatment by sub-grouping.

c. P-value for non-zero slope to dose-response analysis of treatment alone.

A10.5.3. Safety

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

A10.5.4. Long-term

Four hundred and two subjects entered the 24-week, long-term, open-label extension to Study 148-102. As of the cut-off date of 3 February 1997, 20 subjects had completed, and 23 subjects had withdrawn (15 for lack of effectiveness, 4 for withdrawal of consent, and 1 each for laboratory abnormality³, protocol violation, and loss to follow-up). Twelve subjects reported vision abnormalities, all but 2 being described as moderate, and none leading to withdrawal. Three additional subjects were listed as discontinuations for serious adverse events, 2 hospitalized for coronary artery disease and one for myocardial infarction. Common adverse events were headache (11%), vasodilation/flushing (10%), and dyspepsia (5%).

A10.6. Summary

These subjects had erectile dysfunction of organic, but otherwise ill characterized, etiology. One-third to one-half of these subjects were able to achieve erections sufficient for sexual intercourse during a 4-week run-in period. In this population of moderately disabled men, whether analyzed by sexual function questionnaire or event log, there were highly statistically significant, internally consistent, and dose-related treatment effects. Treatment effects were consistent across classes of etiology, presence or absence of nocturnal erections, duration of erectile dysfunction, and history of previous treatment for erectile dysfunction, but the data are indicative of a reduced effect in subjects with diabetes mellitus.

³. Elevated PSA.

Study 148-103: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male patients with erectile dysfunction.

NDA 20-895
Sildenafil for male impotence

A11. Study 148-103: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male patients with erectile dysfunction.

A11.1. Source documents Study protocol INL vol 15.1; study report: NDA vol 1.95-1.97; electronic document: 46289525.pdf; SAS datasets.

A11.2. Investigators Multi-center study with 20 investigators in the United States.

A11.3. Study dates 24 April 1996 to 18 November 1996.

A11.4. Study design This study description was based upon the protocol dated 28 February 1996. There were no amendments

Drug supplies are shown in Table 81 below.

Table 81. Drug supplies (Study 148-103).

	Lot		Lot
Placebo 25 mg	4469-101A-G1	Sildenafil 25 mg	4469-120A-G1
Placebo 50 mg	4469-104-G1	Sildenafil 50 mg	4469-121A-G1
Placebo 100 mg	4469-084-G1	Sildenafil 100 mg	4469-119A-G1

The intent was to randomize 230 male subjects age >18, with erectile dysfunction¹ 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, other experimental drug use within 3 months, or (17) 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 to placebo or sildenafil 50 mg and followed for 12 weeks. A 1:1 placebo:active randomization was implemented, although there were expected differences in the rate of withdrawal for lack of efficacy. 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. At any visit, subjects who were intolerant of the starting dose could have the dose halved and tolerant subjects with inadequate efficacy could have the dose doubled. 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

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

efficacy questions), and a quality of life questionnaire. Optionally, partners filled out another questionnaire.

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

The study was sized to achieve 90% power at $\alpha=0.05$ to detect a treatment effect the same size as seen in a previous study. 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 not 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". 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:

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.

A11.5. Results

A11.5.1. Conduct

Three hundred and sixty-eight subjects were screened, 329 were randomized, and 307 (93%) completed study. Individual sites enrolled 9 to 23 subjects.

Demographics of the 2 treatment groups are shown in Table 82 below. About 56% of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 11% had used non-drug treatments.

Protocol violations are described in Table 83 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 82. Demographics (Study 148-103).

		Placebo N=166	Sildenafil N=163			Placebo N=166	Sildenafil N=163
Race (%)	White	93	95	Duration (y)	Mean	4.7	5.0
	Black	5.4	2.5		Range	0.6-26	0.5-26
	Other	1.8	2.5				
Age	Mean	59	60	Med hx (%)	Hypertension	31	28
	Range	31-81	26-79		Diabetes	11	8.0
Etiology (%)	Organic	63	55		Prostatectomy	20	18
	Psychogenic	16	14		Depression	5.4	7.4
	Mixed	22	31		IHD	11	21

Table 83. Protocol violations (Study 148-103).

At randomization		On treatment	
	n		n
Prohibited meds	33	>1 dose/day	34
Baseline lab abn	4	Blind broken for AE	8
Peyronie's disease or anatomic defect	7		
Active medical problem	5		
Ethanol or drug abuse	6		
Confounding condition/treatment	6		
Poorly controlled hypertension	5		
Total ^a	55		

a. Some subjects had more than one violation.

The disposition of subjects in the trial is shown in Figure 33 below, which shows the placebo group in the left panel and the active treatment group in the right panel. Most subjects remained in study for more than 12 weeks, but some "completed" several weeks early. As the sponsor predicted, fewer subjects on active treatment withdrew for lack of efficacy (or withdrew consent).

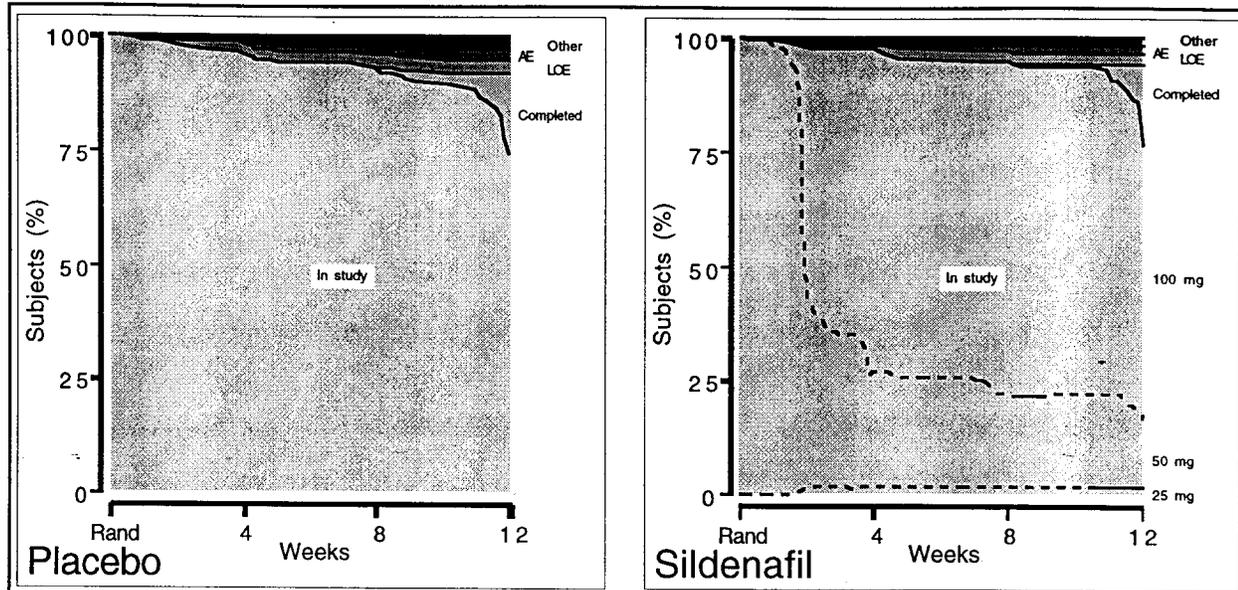


Figure 33. Disposition of subjects (Study 148-103).

The reviewers counted all subjects as “in study” until they reach a state in an all-inclusive set of mutually exclusive final states. In this particular case, the band labeled “LOE” (lack of efficacy) includes subjects who withdrew consent, the band labeled “AE” (adverse event) includes subjects withdrawn for laboratory abnormalities, and the “Other” band includes subjects withdrawn for protocol violations and subjects lost to follow-up. The dashed lines through the “in study” area of the active treatment group show the proportion of subjects on each dose.

A11.5.2. 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, 1 for never or rarely successful, etc., up to 5 for always or almost always successful. The sponsor’s analyses were LOCF, which tends to make placebo, which had a higher withdrawal rate, better than it otherwise would be. Results are summarized in Table 84 below.

Table 84. ITT analyses of IIEF questions 3 and 4 (Study 148-103).

		Placebo N=166		Sildenafil N=163		P
		n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	2.0 ^a	—	—	<0.0001
	Week 12	138	2.3	138	3.9	
How often were you able to maintain your erection after penetration?	Baseline	—	1.5	—	—	<0.0001
	Week 12	138	1.8	137	3.6	

a. Pooled baseline value for all subjects.

Secondary end points from the other IIEF questions are described in Table 85 below (sponsor’s analyses only). All treatment effects were highly statistically significant, except for one pertaining to sexual desire, for which there appeared to be no treatment effect.

About 22% of placebo and active group partners responded on the partner questionnaire. There were statistically significant treatment effects, at 12 weeks, on questions to rate the partner’s erections and satisfaction of sexual intercourse.

Table 85. ITT analyses of non-primary IIEF questions at week 12 (Study 148-103)^a.

Domain	Question	Base-line	Placebo N=166		Sildenafil N=163		P
			n	Q	n	Q	
Erectile function	Able to get erection	2.4	138	2.4	138	3.9	<0.0001
	Erections hard enough	2.0	138	2.1	138	3.8	<0.0001
	Difficulty maintaining erection	1.6	138	1.9	138	3.7	<0.0001
	Confidence in erection	1.6	137	1.9	136	3.3	<0.0001
Intercourse satisfaction	Attempted intercourse	2.2	139	2.9	138	3.5	<0.0001
	Satisfaction of intercourse	1.8	139	2.0	138	3.7	<0.0001
	Enjoyment of intercourse	1.9	139	2.2	138	3.6	0.0001
Orgasmic function	Frequency of ejaculation	2.8	139	2.8	134	3.9	<0.0001
	Frequency of orgasm	2.7	139	2.9	138	3.8	<0.0001
Sexual desire	Frequency of desire	3.6	138	3.5	138	3.5	0.7
	Rating of desire	3.3	139	3.3	138	2.5	0.006
Overall satisfaction	Satisfaction with sex life	1.8	138	2.0	138	3.7	<0.0001
	Satisfaction with relationship	2.6	138	2.8	137	4.0	<0.0001

a. Sponsor's analyses.

The global assessment by subjects whether treatment improved their erections, the original primary end point, was answered in the affirmative at week 12 by 16% on placebo and 74% on sildenafil, a highly statistically significant difference.

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. Table 86 below shows the reviewers' analyses.

Table 86. Successful intercourse by event logs (Study 148-103).

	Placebo N=166	Sildenafil N=163
Attempts		
Total	5645	5971
Per subject mean	34	37
Successes		
Total	732	2792
Per subject mean	4.4	17.1
Success by attempts (%)	13	47
Success by subjects (%)		
During run-in	37	32
During DB treatment	55	87

Several quality of life questions demonstrated a nominally highly statistically significant treatment effect—health compared to a year ago, satisfaction with relationship, impact of erectile problems—but the treatment effect size was, in each case, small.

The reviewers analyzed the proportion of subjects improving, staying the same, or worsening, on the primary effectiveness questions, by treatment group, at week 24, as shown in Table 87 below.

Table 87. ITT shift analyses of IIEF questions 3 and 4 at week 24 (Study 148-103).

		Placebo N=161	Sildenafil N=158
How often were you able to penetrate your partner?	Decr (%)	25	3
	Same (%)	41	22
	Incr (%)	34	75
How often were you able to maintain your erection after penetration?	Decr (%)	20	6
	Same (%)	48	15
	Incr (%)	32	79

The reviewers also carried out an analysis of the primary end point on sub-groups defined by etiology of erectile dysfunction, duration of erectile dysfunction, history of nocturnal erections, history of prior treatment for erectile dysfunction, and history of diabetes mellitus. The results of ANCOVA analyses of the sildenafil-placebo difference in score, after adjustment for baseline and age, are summarized in Table 88 below. The results are consistent with there being similar treatment effects regardless of classification of etiology, presence or absence of nocturnal erections, previous use of drugs or devices for treatment of erectile dysfunction, duration of erectile dysfunction, or history of diabetes.

Table 88. Sub-group analyses of IIEF questions 3 and 4^a (Study 148-103).

	N	How often were you able to penetrate your partner?			How often were you able to maintain your erection after penetration?				
		Factors ^b	Pcbo	Sil	P	Factors	Pcbo	Sil	P
Etiology		Baseline				Baseline			
Organic	193	Etiology	0.1	1.6	0.0001	Etiology	0.2	1.9	0.0001
Psychogenic	49		0.2	2.3	0.0001		0.3	2.4	0.0001
Mixed	87		0.4	1.9	0.0001		0.4	2.2	0.0001
Nocturnal erections		Baseline				Baseline			
Yes	202	Noct	0.2	1.9	0.0001	Noct	0.3	2.2	0.0001
No	102		0.6	2.0	0.0001		0.4	2.0	0.0001
Unknown	25		0.0	0.9	0.19		0.0	1.5	0.04
Duration		Baseline				Baseline			
<3 years	132	Age	0.4	1.7	0.0001	Age	0.3	2.1	0.0001
>3 years	197		0.1	1.9	0.0001		0.2	2.1	0.0001
Previous treatment		Baseline				Baseline			
Yes	230	Age	0.1	1.9	0.0001	Age	0.2	2.1	0.0001
No	99		0.3	1.5	0.0001		0.3	1.9	0.0001
Diabetes mellitus		Baseline				Baseline			
Yes	31	Age	0.6	1.6	0.07	Age	0.3	1.6	0.02
No	298		0.2	1.8	0.0001		0.3	2.1	0.0001

a. Reviewers' LOCF analyses; sildenafil-placebo difference in score, after adjustment for baseline and age, classified as <55 or >55.

b. Statistically significant effects ($P < 0.05$) by ANCOVA from among baseline score, age classified as <55 or >55, sub-grouping (etiology, etc.), treatment by age (Tx*age) interaction, or treatment by sub-grouping.

A11.5.3. Safety

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

A11.5.4. Long-term

Two hundred and twenty-five subjects entered the 36-week, long-term, open-label extension to Study 148-103. As of the cut-off date of 3 February 1997, 0 subjects had completed, and 18 subjects had withdrawn (8 for lack of effectiveness, 2 for headaches, 1 for headache and abdominal pain, 1 for blurred vision and facial flushing,

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1 for prostate cancer, 3 for withdrawal of consent, and 1 each for laboratory abnormality² and protocol violation). Eleven subjects reported vision abnormalities, generally described as moderate, with one contributing to withdrawal. Two additional subjects are listed as discontinuations for serious adverse events, one subject hospitalized for CHF and one for dyspnea; the latter died 3 months after discontinuation. Common adverse events were headache (12%), vasodilation/flushing (10%), and dyspepsia (5%).

A11.6. Summary

One-third of subjects were able to attain and maintain an erection sufficient for sexual intercourse during a 4-week baseline period. In this population of moderately disabled men, with largely organic, but otherwise ill-characterized, erectile dysfunction, whether analyzed by sexual function questionnaire or event log, there were highly statistically significant and internally consistent treatment effects. There was a strong tendency to migrate to the highest available dose.

² Elevated alkaline phosphatase.

A12. Study 148-104: A double-blind, randomized, placebo-controlled, parallel group, multicenter, flexible dose escalation study to assess the efficacy and safety of sildenafil administered as required to male diabetic patients with erectile dysfunction.

- A12.1. Source documents** Study protocol IND vol 15.1; study report: NDA vol 1.108-1.110; electronic document: 46132596.pdf; SAS datasets.
- A12.2. Investigators** Multi-center study with 19 investigators in the United States.
- A12.3. Study dates** 2 May 1996 to 14 November 1996.
- A12.4. Study design** This study description was based upon the protocol dated 28 February 1996. There were no amendments

Drug supplies are shown in Table 89 below.

Table 89. Drug supplies (Study 148-104).

	Lot		Lot
Placebo 25 mg	4469-101A-G1	Sildenafil 25 mg	4469-120A-G1
Placebo 50 mg	4469-104-G1	Sildenafil 50 mg	4469-121A-G1
Placebo 100 mg	4469-084-G1	Sildenafil 100 mg	4469-119A-G1 4469-119B-G1

The intent was to randomize 230 male subjects age >18, with erectile dysfunction¹ of >6 months' duration, diabetes mellitus type I for >5 years or type II for >2 years, and in a heterosexual relationship for >6 months. Diabetes was to be stable for at least 3 months, with glycated hemoglobin <12%, and screening fasting glucose <300 mg/dL. 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, active diabetic retinopathy, history of serious hypoglycemia within 6 months, severe autonomic neuropathy, ketoacidosis within 3 years, or diabetes secondary to pancreatic damage, Cushing's disease, or acromegaly, (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, other experimental drug use within 3 months, or (17) 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 to placebo or sildenafil 50 mg and followed for 12 weeks. A 1:1 placebo:active randomization was implemented, although there were expected differences in the rate of withdrawal for lack of efficacy. 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. Each question was to be analyzed separately with p<0.05 on both necessary for demonstrating efficacy. Subjects

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

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.

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

The study was sized to achieve 90% power at $\alpha=0.05$ to detect a treatment effect the same size as seen in a previous study. 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 not 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". 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:

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.

A12.5. Results

A12.5.1. Conduct

Three hundred and fifty-five subjects were screened, 268 were randomized, and 252 (94%) completed study. Individual sites randomized 6 to 31 subjects.

Demographics of the 2 treatment groups are shown in Table 90 below. About 38% of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 11% had used non-drug treatments.

Table 90. Demographics (Study 148-104).

		Placebo N=132	Sildenafil N=136			Placebo N=132	Sildenafil N=136
Race (%)	White	76	81	Duration (y)	Mean	5.8	5.0
	Black	14	12		Range	0.6-22	0.5-26
	Other	9.8	7.4				
Age	Mean	57	57	Med hx (%)	Diabetes I	21	16
	Range	27-79	33-76		Diabetes II	79	84
Etiology (%)	Organic	96	95		Hypertension	51	53
	Psychogenic	0	0		IHD	25	27
	Mixed	3.8	5.1		Prostatectomy	7.6	4.4
					Periph vasc dis	7.6	3.7

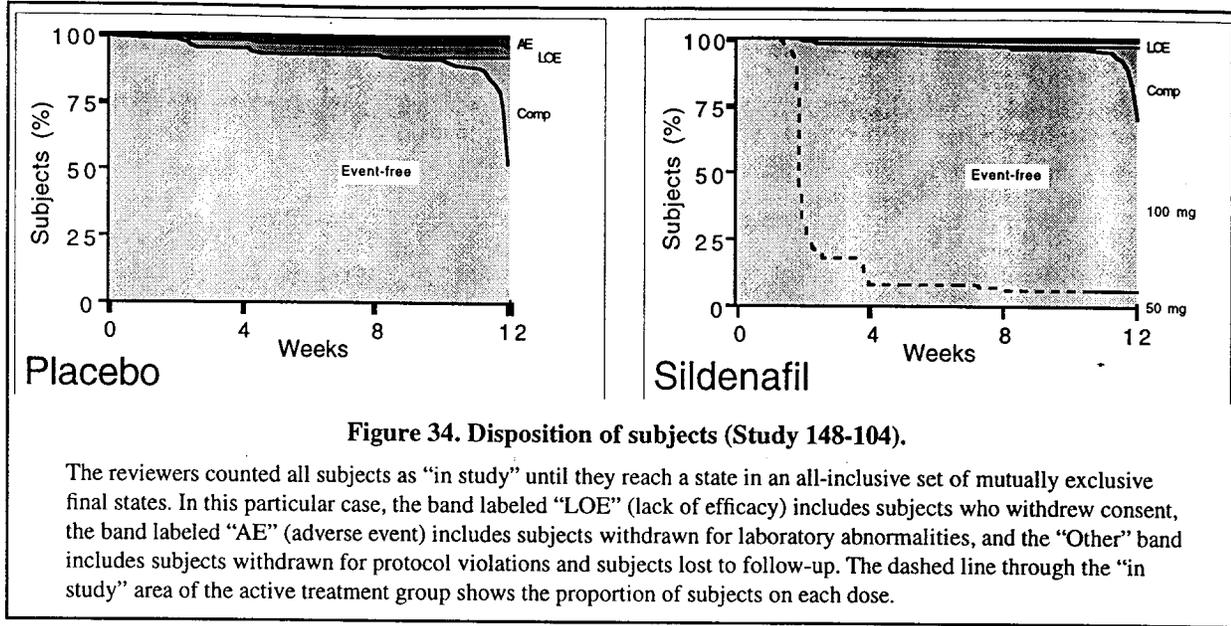
Protocol violations are described in Table 91 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 91. Protocol violations (Study 148-104).

At randomization		On treatment	
	n		n
Prohibited meds	16	>1 dose/day	19
Baseline lab abn	11	Blind broken for AE	2
Diabetes diagnosis < 2 years	1	Mis-dosed	2
Active medical problem	25		
Ethanol or drug abuse	11		
Confounding condition/treatment	9		
Poorly controlled hypertension	4		
Total ^a	75		

a. Some subjects had more than one violation.

The disposition of subjects in the trial is shown in Figure 34 below, which shows the placebo group in the left panel and the active treatment group in the right panel. Most subjects remained in study for more than 12 weeks, but some "completed" several weeks early. As the sponsor predicted, fewer subjects on active treatment withdrew for lack of efficacy (or withdrew consent).



A12.5.2. 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, 1 for never or rarely successful, etc., up to 5 for always or almost always successful. The reviewers’ ITT analyses included all randomized subjects, assigning a worst rank to subjects with no assessment post-randomization². Both the sponsor’s and the reviewers’ analyses were LOCF, which tends to make placebo, which had a higher withdrawal rate, better than it otherwise would be. Results are summarized in Table 92 below.

Table 92. ITT analyses of IIEF questions 3 and 4 (Study 148-104).

		Placebo N=132		Sildenafil N=136		P
		n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	1.7 ^a	—	—	<0.0001
	Week 12	126	2.0	131	3.2	
How often were you able to maintain your erection after penetration?	Baseline	—	1.4	—	—	<0.0001
	Week 12	125	1.6	131	2.9	

a. Pooled baseline value for all subjects.

Secondary end points from the other IIEF questions are described in Table 93 below (sponsor’s analyses only). All treatment effects were highly statistically significant, except for one pertaining to sexual desire, for which there appeared to be no treatment effect.

About 20% of placebo and active group partners responded on the partner questionnaire. There were no statistically significant treatment effects, at 12 weeks, on questions to rate the partner’s erections and satisfaction of sexual intercourse, although the trend is in favor of active treatment.

The global assessment by subjects whether treatment improved their erections, the original primary end point, was answered in the affirmative at week 12 by 10% on placebo and 57% on sildenafil, a highly statistically significant difference.

². Worst rank for all withdrawals?

Table 93. ITT analyses of non-primary IIEF questions at week 12 (Study 148-104)^a.

Domain	Question	Base-line	Placebo N=166		Sildenafil N=163		P
			n	Q	n	Q	
Erectile function	Able to get erection	2.0	126	1.8	131	3.1	<0.0001
	Erections hard enough	1.6	126	1.8	131	3.1	<0.0001
	Difficulty maintaining erection	1.3	127	1.6	131	2.7	<0.0001
	Confidence in erection	1.5	127	1.6	131	2.5	<0.0001
Intercourse satisfaction	Attempted intercourse	2.0	126	2.7	131	3.4	<0.0001
	Satisfaction of intercourse	1.5	127	1.7	131	2.7	<0.0001
	Enjoyment of intercourse	1.7	126	1.8	131	2.8	<0.0001
Orgasmic function	Frequency of ejaculation	2.9	127	3.3	131	3.9	0.0006
	Frequency of orgasm	2.9	127	3.3	131	3.7	0.02
Sexual desire	Frequency of desire	3.6	127	3.7	131	3.7	0.7
	Rating of desire	3.3	127	3.4	131	3.5	0.2
Overall satisfaction	Satisfaction with sex life	1.8	127	2.1	131	2.9	<0.0001
	Satisfaction with relationship	2.5	127	2.8	130	3.3	0.001

a. Sponsor's analyses.

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. Table 94 below shows the reviewers' analyses.

Table 94. Successful intercourse by event logs (Study 148-104).

	Placebo N=132	Sildenafil N=136
Attempts		
Total	3763	4746
Per subject mean	29	35
Successes		
Total	270	1439
Per subject mean	2.0	11
Success by attempts (%)	7.2	30
Success by subjects (%)		
During run-in	17	22
During DB treatment	32	72

Several quality of life questions demonstrated a nominally highly statistically significant treatment effect—mental health, impact of erectile problems—but the treatment effect size was, in each case, small.

A12.5.3. Safety

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

A12.5.4. Long-term

One hundred and eighty-five subjects entered the 36-week, long-term, open-label extension to Study 148-104. As of the cut-off date of 3 February 1997, 0 subjects had completed, and 22 subjects had withdrawn (16 for lack of effectiveness, 1 each for leg pain, bloodshot eyes and heartburn, and dizziness and hypertension, and 1 each for protocol violation, leaving country, and withdrawal of consent). Three subjects reported vision abnormalities, none contributing to withdrawal. Three other subjects are listed as discontinuing for serious adverse events (3 for coronary artery disease, one

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of whom died, and 1 for transient ischemic attack). Common adverse events were headache (6%) and vasodilation/flushing (8%).

A12.6. Summary

One-fifth of these subjects with well-controlled diabetes mellitus had erections sufficient for sexual intercourse during a 4-week baseline assessment period. Whether analyzed by sexual function questionnaire or event log, there were highly statistically significant and internally consistent treatment effects. There was a strong tendency to migrate to the highest available dose.

Study 148-105: A double-blind, randomised, placebo controlled, four-way crossover study to investigate the efficacy, safety and toleration of single oral dose of sildenafil (25, 50, and 100 mg) in patients with male erectile dysfunction.

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A13. Study 148-105: A double-blind, randomised, placebo controlled, four-way crossover study to investigate the efficacy, safety and toleration of single oral dose of sildenafil (25, 50, and 100 mg) in patients with male erectile dysfunction.

- A13.1. Source documents** Study protocol NDA 20-895, vol 1.111; study report: NDA vol 1.111; electronic document: 46004687.pdf.
- A13.2. Investigators** Multi-center study with 2 investigators in the United States.
- A13.3. Study dates** 13 August 1996 to 27 November 1996.
- A13.4. Study design** This study description was based upon the protocol dated 12 June 1996. There were no amendments

Drug supplies are shown in Table 95 below.

Table 95. Drug supplies (Study 148-105).

	Lot		Lot
Placebo 25 mg	4469-101A-G1	Sildenafil 25 mg	4469-144-G1
Placebo 50 mg	4469-104-G1	Sildenafil 50 mg	4469-142B-G1
Placebo 100 mg	4469-084-G1	Sildenafil 100 mg	4469-119C-G1

The intent was to randomize 48 male subjects age >18, with erectile dysfunction¹ 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) hypoactive sexual drive, (3) elevated prolactin or low testosterone, (4) major psychiatric illness, (5) history of alcohol or drug abuse, (6) major hematologic, renal, or hepatic disease, (7) spinal cord injury, (8) poorly controlled diabetes, (9) stroke or myocardial infarction within 6 months, (10) cardiac failure, unstable angina, or life-threatening arrhythmia within 6 months, (11) blood pressure outside 90/50 to 170/100 mmHg, (12) active peptic ulcer disease, (13) bleeding disorder, (14) baseline lab abnormality, (15) recent changes in medication associated with erectile dysfunction, (16) regular use of nitrates, androgens, or trazodone, (17) other medical or social problems limiting participation, (18) other treatment of erectile dysfunction, (19) experimental drug use within 3 months, (20) blood donation within 1 month, and (21) retinitis pigmentosa.

Subjects had routine safety evaluations carried out at a screening visit. They then received single doses of placebo or study drug 25, 50, or 100 mg in random order on clinic visits separated by at least 7 days. Penile plethysmography was performed in the setting of a 20-minute videotape of sexual activity and for the following hour. Plasma samples were obtained at baseline and at 90 minutes.

The primary end point was the log-transformed duration of 60% rigidity². The log-transformed duration of 80% rigidity was a secondary end point.

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

A13.5. Results

- A13.5.1. Conduct** Fifty-seven subjects were screened, 54 were randomized, and 53 (98%) completed study.

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

² The sponsor cites studies to show that 60% rigidity is thought adequate for penetration.

Demographics of the 4 treatment groups were similar: mean ages ranged from 51 to 55 years. All but 3 subjects were Caucasian. Etiology of erectile dysfunction was organic in 48%, psychogenic in 20%, and mixed in 31%.

Protocol violations included anatomical defects (1), prohibited medication (1), history of drug abuse (5). None of these subjects were excluded from the sponsor's 'evaluable subjects' analyses.

One subject discontinued after the 25-mg dose, for treatment-related facial flushing and vertigo.

A13.5.2. Effectiveness

The sponsor's results of ITT analysis of the primary end point are summarized in Table 96 below. No statistically significant effect was seen in the duration of 80% rigidity.

Table 96. ITT analyses of Rigiscan data (Study 148-105).

	Placebo N=54	Sildenafil			P
		25 mg N=54	50 mg N=53	100 mg N=53	
Duration of 60% rigidity (min)	0.06	0.53	0.39	0.95	0.0002

A13.5.3. Pharmacokinetics

Approximately dose-proportional plasma levels of sildenafil were seen at 60 and 90 minutes after dosing, as shown in Table 97 below. Plasma levels of the principal metabolite, UK-103,320, were about 40% as high as for the parent drug, and were also approximately dose-proportional.

Table 97. Plasma levels (±SD) of sildenafil (Study 148-105).

	25 mg	50 mg	100 mg
60 min	96±43	194±128	426±219
90 min	81±39	200±129	370±167

The reviewers performed no analyses of these data.

A13.5.4. Safety

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

A13.6. Summary

The study population appeared to similar to that studied for effects on sexual performance. Dose-related effects were found on duration of erections, but the durations attained in the clinic were small.