

Center for Drug Evaluation and Research

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Appendix A52, page 212 through Appendix A56, page 224

A52. Study 148-364: A double-blind, randomised, placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of fixed doses of sildenafil administered for three months to male patients with erectile dysfunction.

A52.1. Source documents Study protocol IND vol 15.2; study report: NDA vol 1.101-1.103; electronic document: 46161691.pdf; SAS datasets.

A52.2. Investigators Multi-center study with 32 investigators in Europe.

A52.3. Study dates 2 May 1996 to 19 November 1996.

A52.4. Study design This study description was based upon the protocol dated 2 February 1995. There was one amendment; apparently the changes were indicated as italicized text in the submitted protocol.

Drug supplies are shown in Table 157 below.

Table 157. Drug supplies (Study 148-364).

	Lot		Lot
Placebo 25 mg	4469-101	Sildenafil 25 mg	4469-120
Placebo 50 mg	4469-066 4469-067	Sildenafil 50 mg	4469-121
Placebo 100 mg	4469-091	Sildenafil 100 mg	4469-122

The intent was to randomize 460 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 25, 50, or 100 mg and followed for 12 weeks. A 1:1:1:1 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. Subjects completed an event log noting time of study drug administration and subsequent sexual activity. Subjects completing study without an adverse event were eligible for participation in an open-label follow-on study.

The primary efficacy assessment was at week 12. At this visit, subjects completed a global assessment question, sexual function questionnaire (containing the primary

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.

Pharmacokinetic data (plasma samples) were collected at weeks 4, 8, and 12.

The study was sized to achieve 90% power at $\alpha=0.05$ to detect a difference of 0.75 on both primary end point questions. 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:

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.

A52.5. Results

A52.5.1. Conduct

Five hundred and sixty-four subjects were screened, 514 were randomized, and 484 (94%) completed study. Individual sites enrolled 4 to 42 subjects.

Demographics of the 2 treatment groups are shown in Table 158 below. About half of all randomized subjects had received some therapy for erectile dysfunction.

Protocol violations are described in Table 159 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Study 148-364: A double-blind, randomised, placebo-controlled, parallel group, multi-centre study to assess the efficacy and safety of fixed doses of sildenafil administered for three months to male patients with erectile dysfunction.

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Table 158. Demographics (Study 148-364).

		Placebo N=127	Sildenafil				Placebo N=127	Sildenafil				
			25 mg N=128	50 mg N=132	100 mg N=127			25 mg N=128	50 mg N=132	100 mg N=127		
Race (%)	White	98	98	99	97	Duration (y)	Mean Range	5.0	4.5	4.6	5.0	
	Black	0	0.8	1.8	0.8			0.6-30	0.5-30	0.5-40	0.5-30	
	Other	1.6	1.6	0	2.4							
Age	Mean	55	55	57	56	Med hx (%)	Hypertension	14	17	11	15	
	Range	20-77	19-74	30-76	25-79			Diabetes	10	7.8	9.8	7.1
Etiology (%)	Organic	46	44	41	39			Prostatectomy	19	14	14	12
	Psychogenic	29	28	36	35			Depression	0.8	1.6	2.3	1.6
	Mixed	24	28	23	25			IHD	2.4	1.6	1.6	0.8

Table 159. Protocol violations (Study 148-364).

At randomization		On treatment	
	n		n
Missing baseline evaluations	20	>1 dose/day	46
Ethanol or drug abuse	1	Baseline ECG abn	6
Lack of consent	4	Prohibited drug use	9
Poorly controlled hypertension	6	Poorly controlled hypertension	2
Low testosterone	1	Mis-dosed	2
		Blind broken for AE	2
		Mis-diagnosed or other	4
Total ^a	33	Total	62

a. Some subjects had more than one violation.

The disposition of subjects in the trial is shown in Figure 70 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).

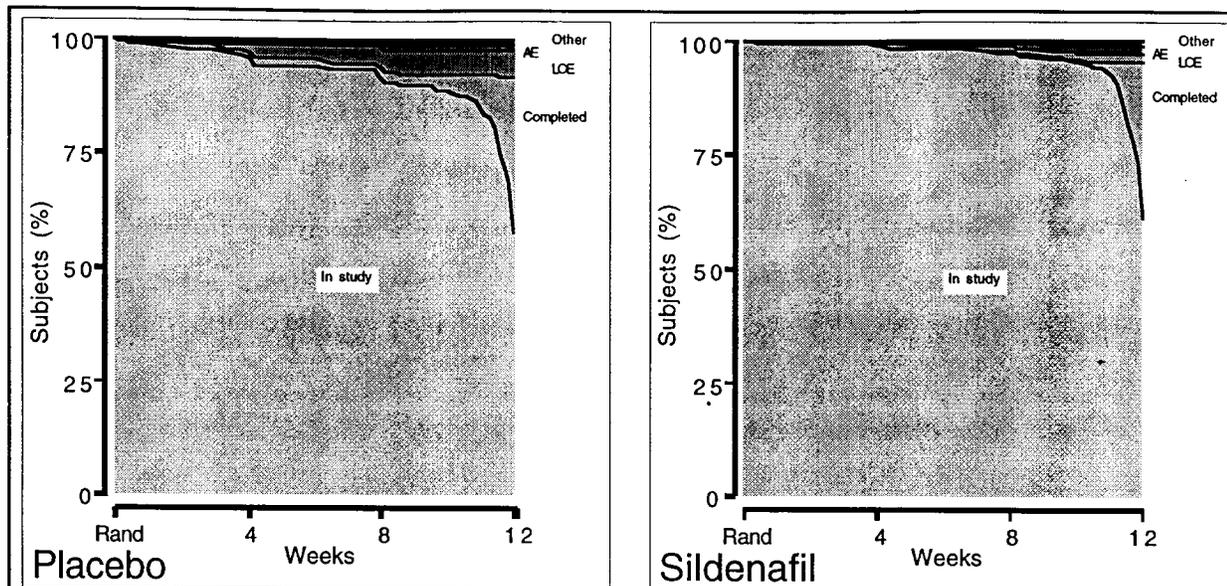


Figure 70. Disposition of subjects (Study 148-364).

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.

A52.5.2. 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 for week 12 are summarized in Table 160 below.

Table 160. ITT analyses of IIEF questions 3 and 4 (Study 148-364).

		Placebo N=127		Sildenafil						P	
				25 mg N=128		50 mg N=132		100 mg N=127			
		n	Q	n	Q	n	Q	n	Q		
How often were you able to penetrate your partner?	Baseline	—	2.2 ^a	—	—	—	—	—	—	—	
	Week 12	117	2.2	121	3.2	123	3.7	120	3.8	<0.0001	
How often were you able to maintain your erection after penetration?	Baseline	—	1.8	—	—	—	—	—	—	—	
	Week 12	115	2.0	119	3.0	122	3.4	118	3.6	<0.0001	

a. Pooled baseline value for all subjects.

Secondary end points from the other IIEF questions are described in Table 161 below (sponsor’s analyses only). All treatment effects were highly statistically significant.

About 1/3 of placebo and active group partners responded on the partner questionnaire at 12 weeks. There were statistically significant treatment effects 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 24% on

Table 161. ITT analyses of non-primary IIEF questions at week 12 (Study 148-364)^a.

Domain	Question	Base-line	Placebo N=127		Sildenafil						P
					25 mg N=128		50 mg N=132		100 mg N=127		
			n	Q	n	Q	n	Q	n	Q	
Erectile function	Able to get erection	2.5	118	2.4	123	3.4	125	3.7	120	3.9	<0.0001
	Erections hard enough	2.2	118	2.2	123	3.3	125	3.6	117	3.9	<0.0001
	Erection maintained to completion	1.7	114	1.9	118	3.1	124	3.6	118	3.6	<0.0001
	Confidence in erection	2.0	117	2.3	120	3.0	123	3.2	117	3.5	<0.0001
Intercourse satisfaction	Attempted intercourse	2.0	114	2.4	120	3.0	123	3.1	117	3.3	<0.0001
	Satisfaction of intercourse	1.9	114	2.1	118	3.1	122	3.5	116	3.8	<0.0001
	Enjoyment of intercourse	2.0	113	2.2	118	2.9	123	3.4	117	3.4	<0.0001
Orgasmic function	Frequency of ejaculation	3.0	118	3.2	118	3.5	121	3.9	120	4.0	<0.0001
	Frequency of orgasm	2.8	118	2.8	117	3.4	121	3.6	119	3.8	<0.0001
Sexual desire	Frequency of desire	3.3	116	3.2	120	3.2	123	3.5	119	3.6	0.001
	Rating of desire	3.1	116	3.1	118	3.2	123	3.3	119	3.4	0.01
Overall satisfaction	Satisfaction with sex life	2.1	118	2.3	118	3.1	123	3.4	117	3.6	<0.0001
	Satisfaction with relationship	2.6	118	2.9	116	3.3	122	3.7	116	3.8	<0.0001

a. Sponsor's analyses.

placebo, 67% on sildenafil 25 mg, 78% on 50 mg, and 86% on 100 mg, 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 162 below shows the reviewers' analyses.

Table 162. Successful intercourse by event logs (Study 148-364).

	Placebo N=127	Sildenafil		
		25 mg N=128	50 mg N=132	100 mg N=127
Attempts				
Total	3705	4313	4192	4062
Per subject mean	29	34	32	32
Successes				
Total	481	1635	1808	1879
Per subject mean	3.8	13	14	15
Success by attempts (%)	13	38	43	46
Success by subjects (%)				
During run-in	32	42	33	31
During DB treatment	53	79	91	82

Among quality of life components, general health and well-being showed small but statistically significant effects, and impact of erectile problems was highly statistically significantly better on sildenafil at 12 weeks.

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 comparisons of the slope of the dose-response curves (change in score per g) are summarized in Table 163 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 and the lack of nominal statistical significance for the slope.

Table 163. Sub-group analyses of IIEF questions 3 and 4^a (Study 148-364).

	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	165		0.1±0.2	13±3	0.0001		0.4±0.2	12±3	0.003
Psychogenic	129		0.3±0.2	15±3	0.0001		0.6±0.2	15±3	0.0001
Mixed	219		0.5±0.2	11±3	0.001		0.6±0.2	12±3	0.003
Nocturnal erections		Baseline				Baseline			
Yes	335	Noct	0.2±0.1	16±2	0.0001	Tx*noct	0.4±0.1	17±2	0.0001
No	151	Tx*noct	0.4±0.2	11±3	0.002		0.7±0.2	8±3	0.02
Unknown	26		1.6±0.5	-11±7	0.15		1.7±0.5	-10±7	0.19
Duration		Baseline				Baseline			
<3 years	177	Duration	0.6±0.2	8±3	0.008	Duration	0.7±0.2	11±3	0.0007
>3 years	336		0.2±0.1	15±2	0.002		0.5±0.1	13±2	0.002
Previous treatment		Baseline				Baseline			
Yes	375		0.4±0.1	12±2	0.0001		0.6±0.1	12±2	0.0001
No	138		0.3±0.2	15±4	0.0001		0.5±0.2	14±3	0.0001
Diabetes mellitus		Baseline				Baseline			
Yes	44	Diabetes	0.3±0.3	2±5	0.72		0.4±0.2	5±4	0.26
No	469		0.4±0.1	14±2	0.0001		0.6±0.1	13±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.

A52.5.3. Safety

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

A52.6. Summary

Erectile dysfunctions were evenly distributed among organic, psychogenic, and mixed etiologies. One-third had erections sufficient for sexual intercourse during the run-in period. Assessed by sexual function questionnaire or event log, there was a highly statistically significant, internally consistent, and dose-related improvement in erectile function at 12 weeks.

Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord.

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A53. Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord.

A53.1. Source documents Study protocol INT vol 15.2; study report: NDA vol 1.121-1.123; electronic document: 46005090.pdf; SAS datasets.

A53.2. Investigators Multi-center study with 19 investigators in Europe and Australia.

A53.3. Study dates 3 June 1996 to 24 January 1997.

A53.4. Study design This study description was based upon the protocol dated 4 March 1996. There were no amendments.

Drug supplies are shown in Table 164 below.

Table 164. Drug supplies (Study 148-367).

	Lot		Lot
Placebo	4469-101	Sildenafil 25 mg	4469-144

The intent was to randomize 150 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, (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 order of receiving placebo or sildenafil 50 mg, with the two 6-week treatment periods separated by a 2-week wash-out period. 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. 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 were to be discontinued, and tolerant subjects with inadequate efficacy could have the dose doubled to 50 or 100 mg. 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 6. 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.

No pharmacokinetic data were collected.

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

The study was sized to achieve 90% power at $\alpha=0.05$ to detect a difference in preference for study drug of 70% vs. 30% for placebo. Randomization was not stratified.

The primary end point was the answer at study end to the question of which treatment was preferred and who indicated that the treatment improved their erections, for subjects with some psychogenic or reflexogenic function. Analysis was to be by logistic regression for binary data. Any interim analyses were not to affect the ongoing trial.

Secondary end points for subjects with some psychogenic or reflexogenic function were (1) responses to the sexual function questionnaire, (2) event log responses, (3) partner responses, and (4) quality of life questionnaire. Secondary end points for all subjects included (1) the preferred treatment, and (2) responses to the sexual function questionnaire.

Pharmacokinetic data were not collected.

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.

A53.5. Results

A53.5.1. Conduct

One hundred and eighty-three subjects were screened, 178 were randomized, and 168 (94%) completed both crossover phases of the study. Individual sites enrolled 1 to 22 subjects.

Demographics of the 2 treatment groups are shown in Table 165 below. About 55% of all randomized subjects had received previous drug therapy for erectile dysfunction, and about 12% had used non-drug treatments.

Table 165. Demographics (Study 148-367).

		First treatment				First treatment	
		Placebo N=89	Sildenafil N=89			Placebo N=89	Sildenafil N=89
Race (%)	White	98	97	Duration (y)	Mean	10.3±8.5	11.7±9.0
	Black	1.1	1.1		Range	0.7-35	0.7-38
	Other	1.1	2.2				
Age	Mean	38	38	Med hx (%)	Urinary tract infection	12	15
	Range	19-63	21-61		Depression	5.6	3.4
Etiology (%)	Central cord	39			Hypertension	4.5	3.4
	Brown-Sequard	2.2			Peripheral vascular disease	2.2	2.2
	Anterior cord	2.2			Ischemic heart disease	2.2	1.1
	Conus medularis	4.5			TURP	1.1	1.1
	Cauda equina	8.4		Diabetes type II	0	1.1	
Unknown or other	43						

Protocol violations are described in Table 166 below. No such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 166. Protocol violations (Study 148-367).

At randomization		On treatment	
	n		n
Prohibited meds	52	>1 dose/day	16
Baseline lab abn	1	Other dosing viol	64
Ethanol or drug abuse	2		
Hypotension	2		
Poorly controlled hypertension	1		
Total ^a	57	Total	80

a. Some subjects had more than one violation.

A53.5.2. Effectiveness

The primary end point was the subject's preference for a treatment, analyzed for subjects with some residual erectile function. Of 145 such subjects who received both treatments, 118 expressed a preference, of whom 111 subjects preferred sildenafil.

Preference for treatment among all subjects was a secondary end point. Of 171 subjects who received both treatments, 134 subjects expressed a preference, and, for 127 subjects, the preference was for sildenafil.

Other secondary end points included the IIEF questions, as described in Table 167 below (sponsor's analyses only). All treatment effects were highly statistically significant.

Table 167. ITT analyses of IIEF questions at weeks 6 and 12 (Study 148-367)^a.

Domain	Question	Subjects with residual erectile function						All subjects					
		Base-line	Placebo		Sildenafil		P	Base-line	Placebo		Sildenafil		P
			n	Q	n	Q			n	Q			
Erectile function	Able to get erection	2.6	132	2.6	130	4.1	<0.0001	2.4	156	2.4	153	4.0	<0.0001
	Erections hard enough	2.6	130	2.4	130	4.0	<0.0001	2.3	155	2.2	154	3.7	<0.0001
	Able to penetrate	2.2	133	2.4	131	4.1	<0.0001	2.0	158	2.2	155	3.8	<0.0001
	Erection after penetration	1.7	133	1.8	131	3.8	<0.0001	1.5	158	1.7	155	3.6	<0.0001
	Erection to completion	1.5	133	1.7	131	3.7	<0.0001	1.4	157	1.6	155	3.5	<0.0001
	Confidence in erection	1.9	132	2.0	131	3.6	<0.0001	1.9	156	1.9	155	3.5	<0.0001
Intercourse satisfaction	Attempted intercourse	1.8	133	2.7	131	3.3	<0.0001	1.6	158	2.6	155	3.2	<0.0001
	Satisfaction of intercourse	1.8	133	2.0	131	3.6	<0.0001	1.6	158	1.9	155	3.5	<0.0001
	Enjoyment of intercourse	1.9	133	2.2	131	3.3	<0.0001	1.8	158	2.1	155	3.2	<0.0001
Orgasmic function	Frequency of ejaculation	1.9	132	1.8	130	2.2	0.002	1.9	155	1.8	152	2.1	0.001
	Frequency of orgasm	1.8	131	1.8	129	2.5	<0.0001	1.8	155	1.8	152	2.5	<0.0001
Sexual desire	Frequency of desire	3.7	133	3.3	131	3.6	<0.0001	3.7	158	3.3	155	3.7	<0.0001
	Rating of desire	3.7	133	3.2	131	3.6	<0.0001	3.7	158	3.3	155	3.6	<0.0001
Overall satisfaction	Satisfaction with sex life	2.7	132	2.5	131	3.9	<0.0001	2.6	157	2.5	155	3.8	<0.0001
	Satisfaction with relationship	3.0	132	3.0	131	4.0	<0.0001	2.9	157	2.9	155	3.9	<0.0001

a. Sponsor's analyses.

About 50% of partners responded on the partner questionnaire. There were statistically significant treatment effects on questions to rate the partner's erections and satisfaction of sexual intercourse.

Study 148-367: A double-blind, randomised, placebo-controlled, two way cross-over, flexible dose study to assess the efficacy and safety of oral doses of sildenafil in patients with erectile dysfunction caused by traumatic injuries to the spinal cord.

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The only aspect of the quality of life assessment nominally showing a treatment effect pertained to the impact of erectile problems.

The sponsor's analysis of the event logs focussed on the proportion of successful attempts at intercourse, but did not describe the number of such attempts by treatment group, or the success rate for subjects. The reviewers did not analyze event log data for this study, either, because of difficulty determining when subjects moved from one crossover period to the other.

A53.5.3. Safety

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

A53.6. Summary

Subjects all had spinal cord injury as the etiology of erectile dysfunction, but with intact spinal cord-mediated reflexes. Other risk factors for erectile dysfunction were rare. The study showed highly statistically significant and internally consistent treatment-related effects on erectile function and sexual performance, as assessed by a sexual function questionnaire and preference for treatment.

Study 148-369: A double blind, randomised, placebo controlled, sequential design, two way crossover study to investigate the duration of action of a single oral dose of sildenafil (100 mg) on penile erectile activity during visual sexual stimulation in

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A54. Study 148-369: A double blind, randomised, placebo controlled, sequential design, two way crossover study to investigate the duration of action of a single oral dose of sildenafil (100 mg) on penile erectile activity during visual sexual stimulation in patients with male erectile dysfunction without an established organic cause.

- A54.1. Source documents** Study protocol NDA 20-895, vol 1.81; study report: NDA vol 1.81; electronic document: 47061829.pdf.
- A54.2. Investigators** Single-center study with 3 investigators in the United Kingdom.
- A54.3. Study dates** 23 July 1996 to 19 December 1996.
- A54.4. Study design** This study description was based upon the final study report, dated 6 August 1997.
- A total of 16 subjects with a 6-month history of erectile dysfunction, but without diabetes or significant vascular disease, age 18 to 65, were to be recruited.
- Subjects underwent two 2-period crossover studies. During each crossover study, subjects received, in random order, single oral doses of placebo or sildenafil 100 mg on study days 7 days apart. In the first study, penile plethysmography accompanied by visual sexual stimulation was undertaken 4 hours after dosing. In the second crossover study, such evaluations were performed 2 hours after dosing, the change being made on the basis of interim findings from the first study. Blood samples for assay of plasma levels of sildenafil and UK-103,320 were obtained before and after plethysmography.
- Routine safety data were recorded.
- A54.5. Results**
- A54.5.1. Conduct** Sixteen subjects were randomized and 15 completed both crossover studies. Fifteen subjects reported spontaneous erections. Minor protocol violations and technical problems were described, but no subject was excluded from analyses.
- A54.5.2. Pharmacokinetics** Mean plasma levels of sildenafil were 123 ng/mL in study 1 and 255 ng/mL in study 2. Corresponding levels of UK-103,320 were 61 and 84 ng/mL, respectively.
- A54.5.3. Pharmacodynamics** Penile plethysmography data (Rigiscan) obtained during presentation of sexual stimulation showed erections with >60% rigidity lasted about twice as long (part I) or 3-times as long (part II) on sildenafil. Thirteen of 16 subjects had grade 3 or 4 erections on sildenafil and 5 subjects had erections on placebo.
- A54.5.4. Safety** Minor adverse events were reported with only headache bearing apparent relationship to active treatment.
- A54.6. Summary** The data are consistent with there being effects of sildenafil on erectile function in subjects with no established organic cause, and that these effects last at least 4 hours, correlating poorly with plasma levels of sildenafil or metabolite.

A55. Study 148-401: Statistical report a psychometric validation of the international index of erectile function (IIEF) in male patients with erectile dysfunction and age-matched controls.

- A55.1. Source documents** Study protocol NDA 20-895, vol 1.115; study report: NDA vol 1.115; electronic document: 46690347.pdf.
- A55.2. Investigators** Single-center study with 1 investigator in the United States.
- A55.3. Study dates** 15 February 1996 to 22 May 1996.
- A55.4. Study design** This study description was based upon the protocol dated 30 November 1995. There were no amendments.
- This study was undertaken to validate the IIEF. Subjects with erectile dysfunction and age-matched controls were administered the IIEF on two clinic visits, 4 weeks apart. No subject received drug treatment.
- A55.5. Results**
- A55.5.1. Conduct** Sixty subjects were screened, and 58 (27 controls and 37 subjects with erectile dysfunction) completed study.
- The mean age was higher in the control group, but there was a greater proportion of subjects over age 65 in the erectile dysfunction group. About 90% were Caucasian. Erectile dysfunction was similar in etiology and duration to other clinical studies.
- A55.5.2. Validation** The results of this study are discussed in the context of the overall validation program, reviewed in *Development and validation of the primary efficacy instrument (International Index of Erectile Function; IIEF)*, on page 87.

A56. Study 148-451: A study to generate sexual function and quality of life data in male subjects who do not have a diagnosis of erectile dysfunction.

- A56.1. Source documents** Study protocol NDA 20-895, vol 1.126; study report: NDA vol 1.126; electronic document: 47081108.pdf.
- A56.2. Investigators** Multi-center study with 3 investigators in United Kingdom.
- A56.3. Study dates** 26 February 1996 to 23 July 1996.
- A56.4. Study design** This study description was based upon a protocol dated 4 December 1995. There is no mention of amendments.
- There was no drug treatment, and no randomization.
- The intent was to obtain sexual function questionnaire data from 100 normal male subjects, age-matched to subjects in Study 148-359¹, in a stable heterosexual relationship for >6 months.
- The sexual function questionnaire (draft IIEF) was administered once in a single clinic visit.
- No safety data were recorded.
- A56.5. Results**
- A56.5.1. Effectiveness** Results pertaining to the validation of the IIEF are discussed in *Development and validation of the primary efficacy instrument (International Index of Erectile Function; IIEF)*. on page 87.
- A56.5.2. Safety** No safety data were collected.

¹. Study 148-359: A 12 week, double blind, placebo controlled, parallel group, multicentre study to evaluate a new sexual function questionnaire in the assessment of the efficacy of sildenafil (UK-92,480) in patients with erectile dysfunction. on page 199.