Center for Drug Evaluation and Research

Viagra (Sildenafil)

"Joint Clinical Review" for NDA-20-895

Appendix A44, page 191 through Appendix A51.6, page 211

A44. 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.

A44.1. Source documents

Study protocol NDA 20-895, vol 1.118; study report: NDA vol 1.118; electronic document: 46870169.pdf.

A44.2. Investigators

Multi-center study with 4 investigators in United Kingdom.

A44.3. Study dates

18 October 1994 to 23 May 1995.

A44.4. Study design

This study description was based upon the protocol dated 30 June 1994. There is no mention of amendments.

Drug supplies are shown in Table 140 below.

Table 140. Drug supplies (Study 148-355).

	Lot		Lot
Placebo	3039-100	Sildenafil 25 mg	3039-135 3039-134 3039-133

The intent was to randomize 36 male subjects age >18, with erectile dysfunction of no established organic cause, of >6 months' duration, but able to attain an erection under some circumstances during a 3-week run-in period, and in a heterosexual relationship. Subjects were excluded for (1) advanced neurological or vascular causes for impotence, (2) history of alcohol abuse, (3) regular use of nitrates, anticoagulants, or aspirin, (4) need for antidepressants or major tranquilizers, (5) history of asthma, eczema, or drug hypersensitivity, (6) family history of bleeding disorder, active peptic ulcer disease, or migraines, (7) significant abnormality on screening lab or physical exam, (8) experimental drug use within 4 months, (9) recent or planned blood donation, or (10) HBsAg positivity.

At the end of a 3-week treatment-free run-in period during which baseline sexual performance data were collected, subjects were randomized to placebo or sildenafil 25 to 75 mg and followed for 4 weeks. Subjects were then switched to the other treatment and again 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) median and minimum time between doses, (2) the number of doses, and (3) the frequency of erections adequate for penetration.

Routine safety data were recorded.

A44.5. Results

A44.5.1. Conduct

Forty-seven subjects were screened, 44 were randomized, and 43 (98%) completed both study phases.

Subjects had a mean age of 53 and all but 4 were Caucasian. The mean duration of impotence was about 3 years. Six subjects had received previous drug treatments for impotence.

Protocol violations included compliance outside targeted range (8) and drug abuse (1). Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

A44.5.2. Effectiveness

The average number of erections adequate for penetration was 1.4 per week on placebo and 4.2 per week on sildenafil. The number of such erections sexually stimulated was 0.8 per week on placebo and 2.4 per week on sildenafil ($p<0.0001$). The average number of doses per week showed a lesser treatment effect—2.6 on placebo and 3.4 on sildenafil ($p=0.001$). After adjustment for a period effect, based on the event log data, the sponsor estimated the odds of successful intercourse on sildenafil to be 12-times higher than on placebo.

Responders were much more likely to say that sildenafil improved erections than to say that placebo did so.

A44.5.3. Safety

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

A44.5.4. Long-term

Documentation is incomplete. Thirty-two subjects entered the 52-week, long-term, open-label extension to Studies 148-355, 148-357, 148-358, 148-359, 148-360, and 166-301 (not reviewed). As of the cut-off date of 3 February 1997, 11 subjects had completed, and 21 subjects had withdrawn (6 for lack of effectiveness, 8 for loss to follow-up, 4 for withdrawal of consent, 1 for headache, and 2 for elevated hepatic transaminases). One subject reported vision abnormalities, not contributing to withdrawal. Common adverse events were headache (n=7), vasodilation/flushing (n=4), and dyspepsia (n=8).

A44.6. Summary

This was a pilot crossover study in subjects with erectile dysfunction of psychogenic etiology. Results were consistent with treatment effects observed in later and larger studies.

A45. Study 148-356: A multi-centre study consisting of a 16-week open, dose-escalation phase followed by an 8-week randomised, double-blind, placebo controlled phase to assess the efficacy and safety of oral doses of UK-92,480 (sildenafil) taken as required by patients with erectile dysfunction.

A45.1. Source documents

Study protocol NDA 20-895, vol 1.124; study report: NDA vol 1.124; electronic document: 46640637.pdf.

A45.2. Investigators

Multi-center study with 15 investigators in United Kingdom, France, and Norway.

A45.3. Study dates

24 November 1994 to 21 November 1995.

A45.4. Study design

This study description was based upon the amended protocol dated 31 August 1994. There were only minor amendments.

Drug supplies are shown in Table 141 below.

Table 141. Drug supplies (Study 148-356).

	Lot		Lot
Placebo	3039-100A	Sildenafil 10 mg	3039-132
		Sildenafil 25 mg	3039-133A 3039-134A 3039-135A

The intent was to randomize 200 male subjects age 18 to 70, with erectile dysfunction of >3 months' duration, but must have had at least one spontaneous or medically-induced erection within 4 weeks of screening. Subjects were excluded for (1) known vascular, neurological, endocrine or anatomical causes of erectile dysfunction, (2) regular use of nitrates, anticoagulants, major tranquilizers, estrogens, antiandrogens, or other drugs possibly contributing to erectile dysfunction, (3) elevated prolactin or low free testosterone, (4) history of major hematologic, renal, or hepatic disease, (5) history of stroke, subarachnoid hemorrhage, bleeding disorder, or peptic ulcer disease, (6) postural hypotension or blood pressure outside 90/50 to 170/110 mmHg, (7) diabetes if poorly controlled or possibly contributory to erectile dysfunction, (8) experimental drug use within 3 months, (9) alcohol abuse, (10) recent or planned blood donation, (11) clinical depression, or (12) other factors which might affect completion of study.

The study consisted of 3 phases. The first phase was a 2-week single-blind run-in period. The second phase was a 16-week open-label, dose titration phase. During this phase, subjects began treatment on sildenafil 10 mg and had opportunities to escalate or reduce the dose as indicated by effectiveness and tolerability step-wise to a maximum of 100 mg. The third and final phase was an 8-week, randomized, double-blind, parallel-group study in which subjects completing phase 2 were randomized to placebo or their optimum dose, as determined in the open-label phase. There was one clinic visit at 4 weeks prior to the final assessment at 8 weeks.

The primary efficacy assessment was at week 8. The primary end point was the proportion of subjects willing to continue to use their randomized treatment, were it available. Other effectiveness data were obtained in an event log and a sexual function questionnaire.

Routine safety data were recorded.

A45.5. Results

A45.5.1. Conduct

Two hundred and ninety-two subjects were screened, 233 were randomized and received open-label treatment, 205 entered double-blind treatment, and 202 (99%) completed study.

The mean age was 54, and all but 2 subjects were Caucasian. The mean duration of erectile dysfunction was 4.9 years. Erectile dysfunction was of psychogenic origin in 40% and of mixed psychogenic and organic origin in 60%. About half had received pervious treatment for erectile dysfunction. The two treatment groups were similar with respect to these attributes.

Eight subjects were discontinued from open-label study because of protocol violations. Other protocol violations appear to have been minor.

Of 31 subjects who withdrew during open-label or double-blind treatment, there was one death, 7 were for lack of effectiveness, and 7 were for adverse events.

A45.5.2. Effectiveness

At the end of the open-label phase 93% of subjects thought study drug had improved erections and 96% thought they would continue its use if it were available. The distribution of subjects on each dose was 1% on 10 mg, 11% on 25 mg, 29% on 50 mg, and 58% on 100 mg.

At the end of double-blind treatment, 40% of subjects on placebo (N=102) said they would continue using that treatment if it were available, compared with 85% randomized to sildenafil (N=93). Twenty-six percent of placebo subjects and 82% of sildenafil subjects said they thought the treatment improved their erections.

From the event logs, placebo subjects experienced a mean of 0.5 erections per week (sufficient for intercourse) compared with 1.4 per week on sildenafil.

The sexual function questionnaire tended to show highly statistically significant effects on questions pertaining to erectile function, but not on effects pertaining to sexual intercourse, although the trend there was in favor of study drug.

A45.5.3. Safety

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

A45.5.4. Long-term

Documentation is incomplete. One hundred and forty-eight subjects entered the 52-week, long-term, open-label extension to Study 148-356. As of the cut-off date of 3 February 1997, 129 subjects had completed, and 19 subjects had withdrawn (2 for lack of effectiveness, 5 for loss to follow-up, and 1 each for left ventricular failure, drowsiness and headache, nasal congestion and pain, testicular seminoma, prostatic carcinoma, and myocardial infarction). Seven subjects reported vision abnormalities, generally described as moderate, with none contributing to withdrawal. Common adverse events were headache (10%), vasodilation/flushing (10%), and dyspepsia (15%).

A45.6. Summary

Subjects had erectile dysfunction of wholly or substantially psychogenic etiology. During the initial open-label phase, most subject migrated to the 100-mg dose. On this responder population, the placebo response rate (interest in continuing randomized treatment) was 40% (26% for belief that treatment improved erections). By all indications, the response rate for sildenafil was much higher.

A46. Study 148-357: A multi-centre, double blind, randomised, placebo controlled, three way crossover study to investigate the efficacy of single oral doses of sildenafil (UK-92,480) in diabetic patients with penile erectile dysfunction.

A46.1. Source documents

Study protocol NDA 20-895, vol 1.119; study report: NDA vol 1.119; electronic document: 46811438.pdf.

A46.2. Investigators

Multi-center study with 2 investigators in United Kingdom.

A46.3. Study dates

2 November 1994 to 11 April 1995.

A46.4. Study design

This study description was based upon the protocol dated 2 August 1994. There is no mention of amendments.

Drug supplies are shown in Table 142 below.

Table 142. Drug supplies (Study 148-357).

	Lot		Lot
Placebo	3039-100	Sildenafil 25 mg	979-12

The intent was to randomize 18 male subjects age >18, with a 5-year history of diabetes, and erectile dysfunction of >6 months' duration. Subjects were excluded for (1) poor diabetic control, (2) significant arterial disease, (3) regular use of nitrates, anticoagulants, or aspirin, (4) need for antidepressants or major tranquilizers, (5) history of asthma, eczema, or drug hypersensitivity, (6) family history of bleeding disorder, active peptic ulcer disease, or migraines, (7) alcohol abuse, or (8) severe, untreated diabetic retinopathy.

In a 3-phase crossover design, subjects received placebo, sildenafil 25 mg, and sildenafil 50 mg in random order. The first dose was administered in the clinic where subjects underwent penile plethysmography (Rigiscan) from 15 minutes prior to dosing to 2 hours post-dosing. Visual sexually stimulating materials were provided. Subjects were then discharged home on that dose and instructed to take study drug once daily, a half hour prior to usual sexual activity, for 10 days, maintaining a diary.

Plasma drug levels were measured during the in-clinic phases.

Routine safety data were recorded. In addition, subjects had assessments of heart rate variation during deep breathing, in response to Valsalva, and in response to standing.

A46.5. Results

A46.5.1. Conduct

Twenty-one subjects were randomized, and 20 (95%) completed all study phases.

Subjects had a mean age of 51 and all but 1 were Caucasian.

Protocol violations included diabetes diagnosed <5 years (4), poor diabetic control (1), and use of a different mode of Rigisan (4).

A46.5.2. Effectiveness

Rigiscan and diary data are summarized in Table 143 below. A greater proportion of subjects on sildenafil than on placebo reported improvement of erections (50%, similar for both doses, vs. 11%).

Sildenafil levels in plasma were dose-proportional at 2 hours. Metabolite UK-103,320 levels were about half as high as those of the parent drug at 2 hours, and also proportional to dose. Higher plasma levels of sildenafil were weakly positively correlated with longer duration and more frequent erections.

Table 143. Effectiveness data (Study 148-357).

	Plcbo	Sildenafil	
		25 mg	50 mg
Rigidity >60% (minutes)			
Base of penis	1.9	3.8	8.4
Tip of penis	1.3	2.7	4.3
Rigidity >80% (minutes)		0.4	1.0
Base of penis	0.4	0.6	0.9
Tip of penis	0.4		
Erections/week	0.6	0.8	1.6

A46.5.3. Safety

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

A46.5.4. Long-term

Documentation is incomplete. Thirty-two subjects entered the 52-week, long-term, open-label extension to Studies 148-355, 148-357, 148-358, 148-359, 148-360, and 166-301 (not reviewed). As of the cut-off date of 3 February 1997, 11 subjects had completed, and 21 subjects had withdrawn (6 for lack of effectiveness, 8 for loss to follow-up, 4 for withdrawal of consent, 1 for headache, and 2 for elevated hepatic transaminases). One subject reported vision abnormalities, not contributing to withdrawal. Common adverse events were headache (n=7), vasodilation/flushing (n=4), and dyspepsia (n=8).

A46.6. Summary

This was a small pilot crossover study in subjects with diabetes mellitus as the likely etiology of their erectile dysfunction. Erectile function was improved in a dose-related manner.

A47. Study 148-358: A two stage, double blind, placebo-controlled study to assess the efficacy and safety of oral doses of sildenafil (UK-92,480) in spinal cord injury patients with erectile dysfunction.

A47.1. Source documents

Study protocol NDA 20-895, vol 1.120; study report: NDA vol 1.120; electronic document: 47062844.pdf.

A47.2. Investigators

Multi-center study with 3 investigators in United Kingdom.

A47.3. Study dates

13 June 1995 to 29 May 1996.

A47.4. Study design

This study description was based upon the protocol dated 13 January 1995. There is no mention of amendments.

Drug supplies are shown in Table 144 below.

Table 144. Drug supplies (Study 148-358).

	Lot		Lot
Placebo	3039-100	Sildenafil 25 mg	3039-135

The intent was to randomize 88 male subjects age 21 to 49, with a 6-month history of spinal cord injury, but having the ability to achieve an erection in response to a vibrator. Subjects were excluded for (1) anatomical defect or vascular or endocrine etiology to erectile dysfunction, (2) drugs associated with erectile dysfunction, (3) major hematologic, renal or hepatic dysfunction, (4) diabetes, (5) history of stroke, subarachnoid hemorrhage, bleeding disorder, or peptic ulcer disease, (6) spinal cord injury above T5 or T6 (because of risk of reflex hypertension in response to vibrator), (7) postural hypotension or blood pressure <90/50 mmHg, (8) regular use of nitrates or anticoagulants, (9) experimental drug use within 3 months, (10) alcohol abuse, (11) other serious medical, psychological, or social conditions apt to interfere with participation, or (12) recent or planned blood donation.

The study consisted of two phases. During the first phase, subjects participated in a double-blind, randomized, single-dose, 2-way cross-over study comparing placebo and sildenafil 50 mg. This study was conducted in the clinic. Subjects received up to 4-minutes of vibratory stimulation 0.5, 1, and 1.5 hours after study drug administration, with erectile function assessed by penile plethysmography (Rigiscan). Plasma drug levels were measured at 2 hours. The 2 study days were separated by at least 3 days. The second phase was a double-blind, randomized, placebo-controlled parallel-group study of home administration over 4 weeks. Subjects kept a diary and subjects and partners completed a sexual function questionnaire. The primary end point was whether subjects were interested in continued use of the drug at the end of 4 weeks.

Routine safety data were recorded.

A47.5. Results

A47.5.1. Conduct

Thirty-four subjects were screened, 27 were randomized, and 24 (89%) completed all study phases.

Subjects had a mean age of 33, a mean of a 6-year history of erectile dysfunction, and all were Caucasian. Spinal cord injury was described as complete (motor and sensory) in 14 subjects. Half of the subjects had previously received drug treatment for erectile dysfunction.

Only minor protocol violations were reported.

A47.5.2. Effectiveness

By questionnaire, treatment improved erections in 7% of subjects on placebo and 75% of subjects on sildenafil. Fifteen percent of subjects on placebo said they would continue to use randomized treatment, compared with 67% on sildenafil. The proportion of successful intercourse attempts was 38% on placebo and 67% on sildenafil. The number of attempts on the two treatments were not described. Subjects on placebo reported a mean of 0.4 erections per week; those on sildenafil reported 1.5 erections per week. The study was too small to yield useful results on the sexual function questionnaire, but the results were not inconsistent with larger studies. During the in-clinic phase, 4% of placebo and 46% of sildenafil subjects achieved erections with >60% rigidity.

A47.5.3. Safety

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

A47.5.4. Long-term

Documentation is incomplete. Thirty-two subjects entered the 52-week, long-term, open-label extension to Studies 148-355, 148-357, 148-358, 148-359, 148-360, and 166-301 (not reviewed). As of the cut-off date of 3 February 1997, 11 subjects had completed, and 21 subjects had withdrawn (6 for lack of effectiveness, 8 for loss to follow-up, 4 for withdrawal of consent, 1 for headache, and 2 for elevated hepatic transaminases). One subject reported vision abnormalities, not contributing to withdrawal. Common adverse events were headache (n=7), vasodilation/flushing (n=4), and dyspepsia (n=8).

A47.6. Summary

This was a small pilot study in subjects with erectile dysfunction resulting from spinal cord injury, but still evidencing reflex activity. By questionnaire and event log, subjects showed treatment related improvements.

A48. 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.

A48.1. Source documents

Study protocol NDA 20-895, vol 1.126; study report: NDA vol 1.126; electronic document: 47081108.pdf.

A48.2. Investigators

Multi-center study with 7 investigators in United Kingdom.

A48.3. Study dates

14 July 1995 to 13 June 1996.

A48.4. Study design

This study description was based upon an undated protocol. An undated amendment permitted titration of sildenafil to 100 mg.

Drug supplies are shown in Table 145 below.

Table 145. Drug supplies (Study 148-359).

	Lot		Lot
Placebo	3509-057	Sildenafil 25 mg	3509-079

The intent was to randomize 100 male subjects age >18, with a 6-month history of erectile dysfunction, erectile dysfunction evidenced by success <2/3 times during run-in period, and in stable heterosexual relationship for >6 months. Subjects were excluded for (1) advanced vascular, neurological, endocrine, or anatomical causes for erectile dysfunction, (2) regular use of nitrates or anticoagulants, (3) history of major hematologic, renal, or hepatic disease, (4) history of stroke, subarachnoid hemorrhage, bleeding disorder, or peptic ulcer disease, (5) experimental drug use within 3 months, (6) alcohol or drug dependence, (7) recent or planned blood donation, (8) significant abnormalities on screening labs or physical exam, or (9) other factors which might impact on ability to complete study.

After a 2- to 4-week treatment-free run-in period, subjects were randomized to placebo or sildenafil 25 mg and followed for 12 weeks, with clinic visits at the end of weeks 2, 4, and 8. At these visits, the dose could be increased to 50 mg if response was considered inadequate, and it could be dropped back to 25 mg if there were intolerable side effects. Effectiveness data included event logs and sexual function questionnaires. The primary end point was the proportion of subjects reporting an improvement in their erections at 12 weeks. Assessment of the sensitivity and specificity of the sexual function questionnaire was a secondary end point.

Routine safety data were recorded.

A48.5. Results

A48.5.1. Conduct

One hundred and twenty-seven subjects were screened, 111 were randomized, and 97 (87%) completed all study phases.

Subjects had a mean age of 56, a mean of a 4.5-year history of erectile dysfunction, and 93% were Caucasian. Erectile dysfunction was described as organic in 21%, psychogenic in 40%, and mixed in 39%. About 2/3 of subjects had pervious treatment for erectile dysfunction, mostly intracavernosal injection.

Protocol violations at baseline included advanced erectile dysfunction (3), >2/3 successes during run-in (1), use of intracavernosal injection during run-in (1). Violations after randomization included >1 dose per day (27), randomized period > 14 weeks (8), and issue of study drug at screening visit (5).

A48.5.2. Effectiveness

By questionnaire, treatment improved erections in 18% of subjects on placebo and 81% of subjects on sildenafil.

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.

A48.5.3. Safety

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

A48.5.4. Long-term

Documentation is incomplete. Thirty-two subjects entered the 52-week, long-term, open-label extension to Studies 148-355, 148-357, 148-358, 148-359, 148-360, and 166-301 (not reviewed). As of the cut-off date of 3 February 1997, 11 subjects had completed, and 21 subjects had withdrawn (6 for lack of effectiveness, 8 for loss to follow-up, 4 for withdrawal of consent, 1 for headache, and 2 for elevated hepatic transaminases). One subject reported vision abnormalities, not contributing to withdrawal. Common adverse events were headache (n=7), vasodilation/flushing (n=4), and dyspepsia (n=8).

A48.6. Summary

The sponsor has used this study for its (secondary end point) assessment of the validity of the sexual function questionnaire used in other major trials, but it is also entirely consistent in its demonstration of treatment effects assessed with that questionnaire, in subjects with psychogenic and organic erectile dysfunction.

A49. Study 148-360: A double-blind, randomised, placebo controlled, two-way crossover study to investigate the onset of action of single oral doses of UK-92,480 (sildenafil) 50mg in patients with penile erectile dysfunction without an established organic cause.

A49.1. Source documents

Study protocol NDA 20-895, vol 1.80; study report: NDA vol 1.80; electronic document: 46063109.pdf.

A49.2. Investigators

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

A49.3. Study dates

5 September 1995 to 13 February 1996.

A49.4. Study design

This study description was based upon the final study report, dated 15 July 1997.

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

Subjects received, in random order, single doses of placebo or sildenafil 50 mg on study days 7 days apart. Subjects underwent a 1-hour penile plethysmography study (base only) accompanied by visual sexual stimulation, beginning 10 minutes after dosing. Blood samples were obtained for assessment of plasma sildenafil and UK-103,320 at the end of plethysmography.

Routine safety data were recorded.

A49.5. Results

A49.5.1. Conduct

Seventeen subjects were randomized and 16 completed both crossover phases of the study. Fifteen subjects reported spontaneous erections. Minor protocol violations and technical problems were described, but no subject was excluded from analyses.

A49.5.2. Pharmacokinetics

Mean plasma levels at 70 minutes after dosing were 255 ng/mL for sildenafil and 94 ng/mL for UK-103,320.

A49.5.3. Pharmacodynamics

Penile plethysmography data (Rigiscan) obtained during presentation of sexual stimulation showed that 14 subjects on sildenafil and 9 subjects on placebo had erections with >60% rigidity. Erections on sildenafil lasted 3.7-fold longer, on average. However, neither the response rate nor the duration of rigidity results represented statistically significant treatment effects.

As shown in Figure 68 below, there was a poor correlation between plasma levels of sildenafil at 70 minutes and the time to or duration of 60% rigidity.

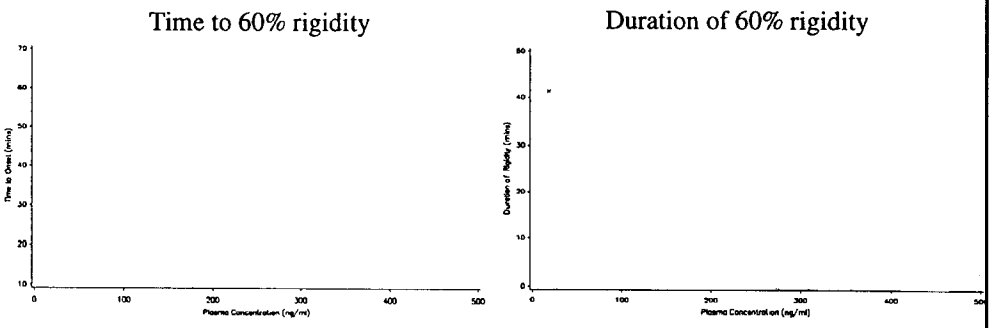

Figure 68. Dependence of erectile response on plasma sildenafil (Study 148-360).

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

A49.5.4. Safety

One subject was hospitalized for paranoid psychosis 9 days after receiving sildenafil. Minor adverse events were reported with no clear relationship to treatment.

A49.5.5. Long-term

Documentation is incomplete. Thirty-two subjects entered the 52-week, long-term, open-label extension to Studies 148-355, 148-357, 148-358, 148-359, 148-360, and 166-301 (not reviewed). As of the cut-off date of 3 February 1997, 11 subjects had completed, and 21 subjects had withdrawn (6 for lack of effectiveness, 8 for loss to follow-up, 4 for withdrawal of consent, 1 for headache, and 2 for elevated hepatic transaminases). One subject reported vision abnormalities, not contributing to withdrawal. Common adverse events were headache (n=7), vasodilation/flushing (n=4), and dyspepsia (n=8).

A49.6. Summary

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

A50. Study 148-361: A 12-week, double-blind, placebo controlled, parallel group, multi-centre study followed by a 40 week open label extension to evaluate the efficacy and safety of UK-92,480 (sildenafil) in patients with erectile dysfunction.

A50.1. Source documents

Study protocol NDA 20-895, vol 1.128; study report: NDA vol 1.128; electronic document: 47062943.pdf.

A50.2. Investigators

Multi-center study with 4 investigators in Australia.

A50.3. Study dates

9 January 1996 to 15 November 1996.

A50.4. Study design

This study description was based upon an undated protocol. There was one minor amendment.

Drug supplies are shown in Table 146 below.

Table 146. Drug supplies (Study 148-361).

	Lot		Lot
Placebo 25 mg	3509-060 3509-057	Sildenafil 25 mg	3509-115 3509-117 3509-080 3509-082 3509-090 3509-135 3509-184 3509-185 3509-136

The intent was to randomize 200 male subjects age >18, with erectile dysfunction 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) spinal cord injury, (4) poorly controlled diabetes or diabetic retinopathy, (5) major hematologic, renal, or hepatic dysfunction, (6) history of stroke or myocardial infarction within 6 months, (7) major psychiatric disorder or alcohol or drug abuse, (8) history of bleeding disorder or peptic ulcer disease, (9) cardiac failure, unstable angina, or life-threatening arrhythmia, (10) postural hypotension or blood pressure outside 90/50 to 170/110 mmHg, (11) clinically significant abnormalities on screening, (12) concomitant drugs associated with erectile dysfunction, (13) regular use of nitrates or anticoagulants, (14) other medical, psychological, or social impediments to study, (15) use of other treatments of erectile dysfunction, (16) experimental drug use within 3 months, and (17) recent or planned blood donation.

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 50, 100, or 200 mg and followed for 12 weeks. Interim visits were scheduled at 2, 4, and 8 weeks. Subjects kept an event log and completed a sexual function questionnaire. Subjects completing study without an adverse event were eligible for a 40-week open-label follow-on study.

The primary end point was the response to IIEF question 1 (*How often were you able to get an erection during sexual activity?*), at 12 weeks.

Routine safety data were recorded.

A50.5. Results

A50.5.1. Conduct

Two hundred and seventy-seven subjects were screened, 254 were randomized, and 241 (95%) completed study.

Demographics of the 4 treatment groups are shown in Table 147 below. Fifty-six percent of subjects had received prior treatment for erectile dysfunction.

Table 147. Demographics (Study 148-361).

		Placebo N=59	Sildenafil 50 mg N=62	Sildenafil 100 mg N=66	Sildenafil 200 mg N=67
Race (%)	White	98	98	97	95
Age	Mean	60	57	57	58
	Range	44-74	32-74	34-77	38-75
Etiology (%)	Organic	49	48	52	46
	Psychogenic	8	5	5	10
	Mixed	41	47	44	43
Duration (y)	Mean	4.9	5.8	5.1	5.1

Twenty-five subjects were randomized in spite of various exclusion criteria, the most common of which were vision abnormalities (10).

A50.5.2. Effectiveness

All randomized subjects with a post-randomization assessment were included in the sponsor's ITT analyses. Responses to IIEF question 1 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-randomization[1]. 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 148 below.

Table 148. ITT analyses of IIEF question1 (Study 148-361).

		Placebo N=59		Sildenafil 50 mg N=62		Sildenafil 100 mg N=66		Sildenafil 200 mg N=67		P
		n	Q	n	Q	n	Q	n	Q	
How often were you able to get an erection during sexual activity?	Baseline	—	2.1[a]	—	—	—	—	—	—	
	Week 12	58	2.1	61	3.8	64	3.8	66	3.9	<0.0001

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

Secondary end points from the other IIEF questions are described in Table 149 below (sponsor's analyses only). All treatment effects were highly statistically significant.

The global assessment by subjects whether treatment improved their erections, the original primary end point, was answered in the affirmative at week 12 by 13% on placebo, and 76 to 78% on sildenafil.

Event log analyses showed a mean of 0.6 erections per week on placebo and 1.4 erections per week on sildenafil (very similar results in the 3 active treatment groups).

1. Worst rank for all discontinuations?

Table 149. ITT analyses of non-primary IIEF questions at week 12 (Study 148-361)[a].

Domain	Question	Base-line	Placebo N=216		Sildenafil 25 mg N=102		50 mg N=107		100 mg N=107		*P*
			n	Q	n	Q	n	Q	n	Q	
Erectile function	Erections hard enough	1.9	58	2.0	61	3.5	64	3.8	66	3.8	<0.0001
	Frequency of penetration	1.9	58	1.9	61	3.4	64	3.7	66	3.7	<0.0001
	Erection maintained to completion	1.7	58	1.9	61	3.3	64	3.7	65	3.7	<0.0001
	Difficulty in maintaining erection	1.6	58	1.7	61	3.2	64	3.5	66	3.6	<0.0001
	Confidence in erection	1.7	57	1.9	61	3.2	64	3.4	65	3.4	<0.0001
Intercourse satisfaction	Attempted intercourse	1.5	58	1.8	61	2.6	64	2.8	66	2.9	<0.0001
	Satisfaction of intercourse	1.8	58	1.9	61	3.4	64	3.7	66	3.6	<0.0001
	Enjoyment of intercourse	1.8	58	1.8	61	2.8	64	3.1	66	3.3	<0.0001
Orgasmic function	Frequency of ejaculation	2.8	55	2.8	61	3.8	63	4.2	65	4.0	<0.0001
	Frequency of orgasm	2.8	55	2.7	61	3.7	63	4.1	65	3.9	<0.0001
Sexual desire	Frequency of desire	3.0	55	3.0	61	3.3	63	3.6	65	3.7	0.0005
	Rating of desire	2.8	56	2.8	61	3.0	63	3.4	66	3.5	0.0004
Overall satisfaction	Satisfaction with sex life	1.9	56	2.0	61	3.2	63	3.4	66	3.5	<0.0001
	Satisfaction with relationship	2.5	56	2.7	61	3.7	63	3.9	66	4.0	<0.0001

a. Sponsor's analyses.

A50.5.3. Safety

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

A50.5.4. Long-term

Documentation is incomplete. Two hundred and twenty-seven subjects entered the 52-week, long-term, open-label extension to Study 148-361. As of the cut-off date of 3 February 1997, 0 subjects had completed, and 7 subjects had withdrawn (4 for lack of effectiveness, 2 for withdrawal of consent, and 1 for sinusitis and hot flushes). Four subjects reported visual disturbances, none of which led to withdrawal. Common adverse events were headache (1%), vasodilation/flushing (4%), and dyspepsia (2%).

A50.6. Summary

Subjects had erectile dysfunction of wholly or substantially organic etiology, excluding spinal cord injury. The primary end point was related to erectile function, but it and the usual secondary end points—other aspects of the sexual function questionnaire and sexual performance by event log—were highly statistically significant, internally consistent, and dose-related. Long-term data are not available.

A51. Study 148-363: A double-blind, randomised, placebo-controlled, parallel group, multi-centre, flexible dose escalation study to assess the efficacy and safety of UK-92,480 administered over six months to male patients with erectile dysfunction.

A51.1. Source documents

Study protocol IND vol 15.2; study report: NDA vol 1.98-1.100; electronic document: 47101479.pdf; SAS datasets.

A51.2. Investigators

Multi-center study with 25 investigators in Europe.

A51.3. Study dates

12 October 1995 to 22 September 1996.

A51.4. Study design

This study description was based upon the protocol dated 10 July 1995. There were two amendments; apparently the changes were indicated as italicized text in the submitted protocol.

Drug supplies are shown in Table 150 below.

Table 150. Drug supplies (Study 148-363).

	Lot		Lot
Placebo	3827-157 3827-158	Sildenafil 25 mg	3827-166 3827-167

The intent was to randomize 300 male subjects age >18, with erectile dysfunction[1] of >6 months' duration, and in a heterosexual relationship for >6 months. Subjects were excluded for (1) anatomical deformities such as severe penile fibrosis, (2) other sexual disorders such as hypoactive sexual desire, (3) elevated prolactin (3x ULN) or low free testosterone (20% below LLN), (4) major, uncontrolled psychiatric disorders, (5) history of alcohol or drug abuse, (6) history of major hematologic, renal, or hepatic disorder, (7) erectile dysfunction following spinal cord injury, (8) uncontrolled diabetes or diabetic retinopathy, (9) stroke or myocardial infarction within 6 months, (10) cardiac failure, unstable angina, ECG ischemia, or life-threatening arrhythmia within 6 months, (11) blood pressure outside 90/50 to 170/100 mmHg, (12) active peptic ulcer disease or bleeding disorder, (13) any clinically significant baseline laboratory abnormality, (14) need for anticoagulants, nitrates, androgens, or trazodone, (15) need for aspirin or NSAIDs and a history of peptic ulcer disease, (16) unwillingness to cease use of vacuum devices, intracavernosal injection, or other therapy for erectile dysfunction, 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 mg and followed for 26 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. 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 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.

No pharmacokinetic data were collected.

The study was sized to achieve 80% power at α=0.05 to detect a difference between a 70% improvement rate on the global assessment on active treatment against a 50% improvement rate on placebo. Randomization was not stratified.

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

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

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

A51.5. Results

A51.5.1. Conduct

Three hundred and seventy-eight subjects were screened, 315 were randomized, and 307 (64%) completed study. Individual sites enrolled 1 to 25 subjects.

Demographics of the 2 treatment groups are shown in Table 151 below. About 71% of all randomized subjects had received some therapy for erectile dysfunction.

Protocol violations are described in Table 152 below. Not all such subjects were excluded from the sponsor's 'evaluable subjects' analyses.

Table 151. Demographics (Study 148-363).

		Placebo N=156	Sildenafil N=159			Placebo N=156	Sildenafil N=159
Race (%)	White	95	97	Duration (y)	Mean	5.1	4.8
	Black	1.9	1.9		Range	1-27	1-35
	Other	3.2	0.6				
Age	Mean	54	55	Med hx (%)	Hypertension	19	21
	Range	23-82	24-77		Diabetes	15	16
Etiology (%)	Organic	30	29		Prostatectomy	12	10
	Psychogenic	32	31		Depression	4.5	8.2
	Mixed	35	38		IHD	6.4	13
	Other	3.8	1.9				

Table 152. Protocol violations (Study 148-363).

At randomization	n	On treatment	n
Missing baseline event log	36	>1 dose/day	51
Ethanol or drug abuse	15	Baseline ECG abn	6
Prohibited drug use	4	Prohibited drug use	8
Poorly controlled hypertension	2	Poorly controlled hypertension	3
		Mis-dosed	1
Total[a]	55	Total	63

a. Some subjects had more than one violation.

The disposition of subjects in the trial is shown in Figure 69 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 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).

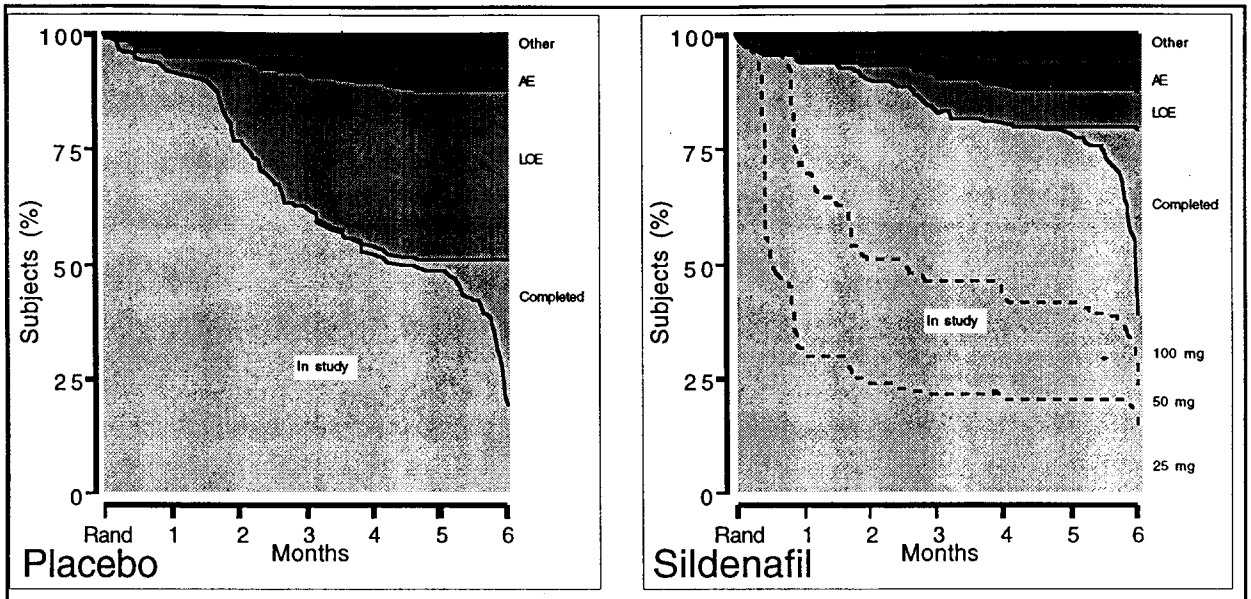

Figure 69. Disposition of subjects (Study 148-363).

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.

A51.5.2. 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 153 below.

Table 153. ITT analyses of IIEF questions 3 and 4 (Study 148-363).

		Placebo N=156		Sildenafil N=159		*P*
		n	Q	n	Q	
How often were you able to penetrate your partner?	Baseline	—	1.9[a]	—	—	
	Week 12	101	2.2	124	3.5	<0.0001
	Week 24	130	2.2	144	3.7	<0.0001
How often were you able to maintain your erection after penetration?	Baseline	—	1.6	—	—	
	Week 12	116	2.1	136	3.5	<0.0001
	Week 24	128	2.1	144	3.6	<0.0001

a. Pooled baseline value for all subjects.

Secondary end points from the other IIEF questions are described in Table 154 below (sponsor's analyses only). All treatment effects were highly statistically significant, except for those pertaining to sexual interest, for which there was at least a trend in favor of increased interest on sildenafil.

About 25% of placebo and active group partners responded on the partner questionnaire at 12 and 26 weeks. There were statistically significant treatment effects, at 12 and 26 weeks, on questions to rate the partner's erections and satisfaction of sexual intercourse.

Table 154. ITT analyses of non-primary IIEF questions at week 12 (Study 148-363)[a].

Domain	Question	Base-line	Week 12					Week 26				
			Placebo N=156		Sildenafil N=159		*P*	Placebo N=156		Sildenafil N=159		*P*
			n	Q	n	Q		n	Q	n	Q	
Erectile function	Able to get erection	2.2	120	2.4	139	3.8	<0.0001	131	2.5	147	3.9	<0.0001
	Erections hard enough	1.9	117	2.1	138	3.6	<0.0001	128	2.2	145	3.7	<0.0001
	Difficulty maintaining erection	1.7	113	2.3	134	3.6	<0.0001	124	2.1	143	3.6	<0.0001
	Confidence in erection	2.0	120	2.2	137	3.4	<0.0001	130	2.2	146	3.4	<0.0001
Intercourse satisfaction	Attempted intercourse	2.1	121	2.7	139	2.9	0.4	131	2.7	146	3.1	0.01
	Satisfaction of intercourse	1.7	121	1.9	136	3.4	<0.0001	131	2.0	143	3.5	<0.0001
	Enjoyment of intercourse	1.9	121	2.2	138	3.0	<0.0001	131	2.1	145	3.1	<0.0001
Orgasmic function	Frequency of ejaculation	2.9	120	2.9	138	3.8	<0.0001	131	3.1	146	3.8	<0.0001
	Frequency of orgasm	2.6	119	2.7	137	3.7	<0.0001	130	2.9	145	3.7	<0.0001
Sexual desire	Frequency of desire	3.2	120	3.4	136	3.6	0.02	131	3.3	145	3.6	0.02
	Rating of desire	3.0	120	3.2	135	3.4	0.08	131	3.2	144	3.4	0.3
Overall satisfaction	Satisfaction with sex life	1.9	120	2.4	138	3.6	<0.0001	130	2.4	147	3.6	<0.0001
	Satisfaction with relationship	2.4	117	2.9	137	3.7	<0.0001	127	2.9	145	3.8	<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 22% on placebo and 82% on sildenafil and at week 26 by 23% on placebo and 80% on sildenafil, both highly statistically significant differences.

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 155 below shows the reviewers' analyses.

Table 155. Successful intercourse by event logs (Study 148-363).

	Placebo N=156	Sildenafil N=159
Attempts		
Total	6984	8978
Per subject mean	45	56
Successes		
Total	1780	5284
Per subject mean	11	33
Success by attempts (%)	25	59
Success by subjects (%)		
During run-in	33	38
During DB treatment	63	89

Among quality of life components, impact of erectile problems was highly statistically significantly on sildenafil at 12 and 26 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 ANCOVA analyses of the sildenafil-placebo difference

in score, after adjustment for baseline and age, are summarized in Table 156 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 156. Sub-group analyses of IIEF questions 3 and 4[a] (Study 148-363).

	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	91	Age	0.7	1.5	0.0001	Age	0.3	2.0	0.0001
Psychogenic	100		0.3	1.5	0.0001		0.3	1.7	0.0001
Mixed	114		0.7	1.7	0.0001		0.2	1.8	0.0001
Other	9		-0.3	3.0	0.03		0.2	1.5	0.36
Nocturnal erections		Baseline				Baseline			
Yes	181	Age	0.3	1.7	0.0001	Age	0.3	1.8	0.0001
No	112		0.1	1.7	0.0001		0.3	1.9	0.0001
Unknown	21		0.5	1.3	0.27		0.3	1.5	0.14
Duration		Baseline				Baseline			
<3 years	134	Age	0.1	1.9	0.0001	Age	0.5	1.6	0.0001
>3 years	180	Tx*duration	0.3	1.4	0.0001	Tx*duration	0.1	1.9	0.0001
Previous treatment		Baseline				Baseline			
Yes	255	Age	0.2	1.7	0.0001	Age	0.2	1.8	0.0001
No	59		0.3	1.5	0.002		0.4	1.6	0.02
Diabetes mellitus		Baseline				Baseline			
Yes	43	Age	0.1	2.1	0.0001	Age	0.0	1.8	0.0001
No	269		0.2	1.6	0.0001		0.3	1.8	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.

A51.5.3. Safety

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

A51.5.4. Long-term

Documentation is incomplete. Two hundred and three subjects entered the 26-week, long-term, open-label extension toStudy 148-363. As of the cut-off date of 3 February 1997, 0 subjects had completed, and 9 subjects had withdrawn (7 for lack of effectiveness, 1 for increased transaminases[2], and 1 for loss to follow-up). One subject reported vision abnormalities, described as severe, but not leading to withdrawal. Common adverse events were headache (6%), vasodilation/flushing (3%), and dyspepsia (2%).

A51.6. Summary

Erectile dysfunction was equally attributable to organic, psychogenic, and mixed etiologies. About one-third of subjects had successful sexual intercourse in the run-in period, and two-thirds of placebo group subjects had some success post-randomization, but one-third of placebo subjects withdrew for lack of effectiveness by 26 weeks. Treatment effects were highly statistically significant and internally consistent in favor of sildenafil at 12 and 26 weeks. Subjects on active treatment distributed approximately equally among the 25-, 50-, and 100-mg doses.

2. Transaminase levels were acutely 3-fold above ULN andreturned to normal range over 2 months.