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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Viagra® / Sildenafil citrate

PROTOCOL NO.: A1481222

PROTOCOL TITLE: A Multicenter, Parallel Group Flexible Dose Study With a Double-Blind, Randomized, Placebo-Controlled Phase and an Open-Label Phase to Evaluate the Quality of Erections in Men With Erectile Dysfunction Treated With Sildenafil Citrate

Study Centers: A total of 25 centers took part in the study and randomized subjects; 6 in Germany, 5 each in Poland, Italy, and Brazil, and 4 in Turkey.

Study Initiation Date and Final Completion Date: 13 May 2005 to 31 January 2006

Phase of Development: Phase 4

Study Objectives:

Primary Objective: The study objective was to evaluate the effect that sildenafil citrate has on the hardness of erections in males with erectile dysfunction, based on subject responses to question 5 on the event log (hardness of erection) as measured at the end of double-blind treatment (Week 6).

Secondary Objectives: The secondary objectives were to assess the efficacy, treatment satisfaction and quality of life changes of sildenafil in men with erectile dysfunction, based on the following assessments as measured at the end of double-blind treatment (Week 6) and at the end of open-label treatment (Week 12):

- Responses to the Quality of Erection Questionnaire (QEQ);
- Responses to International Index of Erectile Function (IIEF) domains (erectile function; orgasmic function; sexual desire; intercourse satisfaction; overall satisfaction);
- Event log success rate variables;
- Responses to the Self Esteem and Relationship (SEAR) Questionnaire (including individual scores for the confidence domain including the sub-domains of self esteem and overall relationship and the sexual relationship domain);

- Responses to Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questionnaire;
- Reponses to the Global Efficacy Assessment Questionnaire (GEAQ);
- Safety and tolerability based on adverse events and other safety assessments.

METHODS

Study Design: This was a parallel group, multicenter, flexible dose study with a double-blind, randomized, placebo-controlled phase and an open-label phase to evaluate hardness of erections and to assess efficacy and satisfaction of sildenafil citrate in men with erectile dysfunction.

The study involved 6 clinic visits over a period of 14 weeks that included a 2-week screening phase, a 6-week double-blind treatment phase with sildenafil citrate or placebo, and a 6-week open-label treatment phase with sildenafil citrate. The maximum exposure to the study drug for an individual subject was 12 weeks.

The visit schedule is presented in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

	Screening	Randomization/ Baseline	DB Dose Adjustment	End DB/ Start OL Treatment	OL Dose Adjustment	Exit
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Study week	**-2**	**0**	**2**	**6**	**8**	**12**
Informed consent	X					
IIEF-EF domain	X					
Inclusion/exclusion criteria	X					
Demography	X					
Medical history	X					
Physical examination	X					
Blood pressure and heart rate	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]
IIEF		X		X		X
SEAR		X		X		X
EDITS				X		X
QEQ		X		X		X
GEAQ				X		X
Adverse events			X	X	X	X
Concomitant drug treatments	X	X	X	X	X	X
Concomitant non-drug treatments/procedures	X	X	X	X	X	X
Assessment for dose adjustment			X		X	
Dispense double-blind sildenafil/placebo		X	X			
Dispense open-label sildenafil				X	X	
Drug accountability			X	X	X	X
Dispense event log worksheets	X	X	X	X	X	
Review event log worksheets		X	X	X	X	X
Subject summary						X

DB = double-blind; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; GEA = Global Efficacy Assessment Questionnaire; IIEF = International Index of Erectile Function; OL = open-label; QEQ = Quality of Erection Questionnaire; SEAR = Self-Esteem and Overall Relationship.

a. Sitting and standing
b. Sitting only.

Number of Subjects (Planned and Analyzed): A total of approximately 300 subjects were planned to be enrolled. For the double-blind phase of this study, 344 subjects were screened and 307 subjects were randomized and enrolled: 96 in Brazil, 73 in Turkey, 66 in Germany, 61 in Poland and 48 in Italy. In the open-label phase of this study, 280 subjects continued treatment with sildenafil (142 subjects previously on sildenafil and 138 subjects previously on placebo).

Diagnosis and Main Criteria for Inclusion: Male subjects, 18–55 years old, with a documented clinical diagnosis of erectile dysfunction confirmed by an IIEF-EF domain score of ≤25. Subjects were excluded from the study if they had been treated with more than 6 doses of sildenafil citrate or any other phosphodiesterase Type 5 inhibitor such as vardenafil or tadalafil for erectile dysfunction.

Study Treatment: Sildenafil and matching placebo tablets were supplied as 25, 50, and 100-mg blue, rounded, diamond shaped, film-coated tablets. Study medication was taken on an outpatient basis. Subjects were instructed to take 1 tablet when required for sexual activity and not more than once daily. The tablet was to be swallowed with a glass of water 30-60 minutes prior to anticipate sexual activity.

Efficacy Endpoints:

Primary Endpoint: The primary efficacy endpoint was the subject's percent erection response of Grades 3 or 4 of erection quality (hardness) to Question 5 from the Event Log at Week 6, which is defined as the change from Baseline to Week 6 Last Observation Carried Forward (LOCF).

Secondary Endpoints: The secondary efficacy endpoints for the double-blind phase were:

- Change from Baseline to Week 6 (LOCF) for QEQ total score (sum of questions Q1, Q3-Q7);
- Change from Baseline to Week 6 (LOCF) for individual questions of the QEQ;
- Change from Baseline to Week 6 (LOCF) for IIEF Q3 and Q4 scores;
- Change from Baseline to Week 6 (LOCF) for IIEF domain scores;
- Change from Baseline to Week 6 (LOCF) for SEAR domain scores;
- Change from Baseline to Week 6 (LOCF) for SEAR questionnaire total score (sum of questions 1-14);
- EDITS Index score (25 multiplied by the average of the subject EDITS items) response at Week 6 (LOCF);
- EDITS Index score dichotomized response at Week 6 (LOCF) (satisfied [>50]/ Unsatisfied [≤50]);
- Responses at Week 6 (LOCF) GEAQ 1 and 2;
- Responses at Week 6 (LOCF) for event log intercourse success rate variables.

The secondary efficacy endpoints for the open-label phase are:

- Change from Week 6 (end of double-blind phase) to Week 12 (LOCF) for QEQ total score (sum of questions Q1, Q3-Q7);
- Change from Week 6 (end of double-blind phase) to Week 12 (LOCF) for individual questions of the QEQ;

- Change from Week 6 (end of double-blind phase) to Week 12 (LOCF) for IIEF Q3 and Q4 scores;
- Change from Week 6 (end of double-blind phase) to Week 12 (LOCF) for IIEF domain scores;
- Change from Week 6 (end of double-blind phase) to Week 12 (LOCF) for SEAR domain scores;
- Change from Week 6 (end of DB phase) to Week 12 (LOCF) for SEAR questionnaire total score (sum of questions 1-14);
- EDITS Index score response at Week 12 (LOCF);
- EDITS Index score dichotomized response at Week 12 (LOCF) (satisfied [>50]/Unsatisfied [≤50]);
- Responses at Week 12 (LOCF) GEAQ 1 and 2;
- Responses at Week 12 (LOCF) for event log intercourse success rate variables.

Safety Evaluations: Safety parameters to be reported were: adverse events, physical examination findings, and vital signs.

Statistical Methods: Two analysis sets were used:

Safety Analysis Set (Population) was defined as subjects who took at least 1 dose of study medication.

Intent-to-Treat (ITT) Analysis Set (population) was defined as subjects who took at least 1 dose of study medication and who provided sufficient efficacy data for at least 1 efficacy analysis.

The criterion of providing sufficient efficacy data for at least 1 efficacy analysis could be satisfied by having either postbaseline data for at least 1 GEAQ or EDITS questionnaire, or baseline and post-baseline data for at least 1 of the following efficacy variables for the erectile dysfunction (ED) subject:

- Individual questions of the QEQ;
- Individual questions of the IIEF Questionnaire;
- Individual questions of the SEAR Questionnaire;
- Efficacy variables derived from the event log.

Analysis of Primary Efficacy Parameter:

The primary efficacy parameter was the change from Baseline for subject's percent erection response on Grades 3 or 4 of erection quality (hardness) to Question 5 from the event log at Week 6. The primary efficacy parameter was analyzed using an analysis of covariance (ANCOVA) model with terms for baseline value, treatment group (sildenafil citrate, placebo), investigator site, and the following prognostic factors: age, duration of ED, and etiology of ED (organic, psychogenetic, and mixed). The final ANCOVA model upon which statistical tests of the treatment comparison, least square (LS) means, and the standard errors were derived as follows: a preliminary "interaction" ANCOVA model including terms for treatment group, investigator site, the 4 covariates listed above, and the 5 2-way interactions between treatment group and site as well as the covariates listed above were used to explore treatment by other factors interactions. If the p-value for the treatment by baseline interaction term for the interaction ANCOVA model was not significant, >0.05, then a "main effect" ANCOVA model consisting of treatment group, investigator site, and the 4 covariates was to be used; otherwise, a "treatment by baseline' ANCOVA model consisting of terms for treatment group, investigator site, the 4 covariates listed above, and the treatment by baseline interaction was used. All other interactions terms were used to explore their effects on treatment, but were not included in the final model on which p-values are based.

Analysis of Secondary Efficacy Parameters:

The analysis for change from Baseline to Week 6 (LOCF) in variables which have scheduled baseline and end of the double-blind phase assessments (ie, secondary efficacy variables based on QEQ, IIEF, SEAR questionnaires) used an ANCOVA model similar to the one described for the primary efficacy variable. The analysis of endpoint EDITS Index at Week 6 used a "main effects" ANCOVA model with terms for treatment, investigator site, and the following prognostic factors: age, duration of ED, and etiology of ED (organic, psychogenetic, and mixed).

The correlation analyses, using Pearson's coefficient, were performed between the percent of erection response of Grades 3 or 4 of erection quality (hardness) to Question 5 from the event log (change from baseline) and:

- IIEF Domains (change from Baseline)
- SEAR total score, domains and sub-domains (change from Baseline)
- EDITS Index (response at Week 6)
- QEQ total score (change from Baseline)

The efficacy data in the open-label treatment phase (Week 6 to Week 12) were summarized by the treatment randomization in the double-blind phase: previous sildenafil and previous placebo. Descriptive statistics (number of subjects [n], mean, standard deviation, median, minimum and maximum) were presented for continuous variables for Week 6, Week 12, and change from Week 6 to Week 12, except EDITS Index score which was summarized at

Week 12 only. Percentage and frequency counts were presented for categorical variables at Week 12.

RESULTS

Subject Disposition and Demography: For the double-blind phase of this study, 344 subjects were screened for enrollment, 307 were enrolled and treated. Of the 154 sildenafil-treated subjects, 142 (92.2%) completed the double-blind treatment phase of the study, and of the 153 placebo-treated subjects, 138 (90.2%) completed the double-blind treatment phase of the study. The most common reason for discontinuation during the double-blind phase was subject default, which included 11 subjects who were no longer willing to participate (2 subjects in the sildenafil groups and 9 in the placebo group) and 5 subjects who were lost to follow-up (3 subjects in the sildenafil group and 2 in the placebo group). Discontinuation due to adverse events occurred in 3 subjects, 1 (placebo, syncope) which was considered to be treatment-related, 2 (sildenafil, right pleural effusion, genital herpes) which were not treatment-related.

For the open-label phase of this study, 280 were enrolled and treated (142 were previously assigned to the sildenafil group and 138 were previously assigned to the placebo group). Of the 142 previously sildenafil-treated subjects, 140 (98.6%) completed the open-label treatment phase of the study, and of the 138 previously placebo-treated subjects, 134 (97.1%) completed the open-label treatment phase of the study. The most common reason for discontinuation during the open-label phase was subject default, which included 3 subjects who were no longer willing to participate (1 subject previously treated with sildenafil and 2 previously treated with placebo) and 2 subjects who were lost to follow-up (1 subject previously treated with sildenafil and 1 previously treated with placebo). There were no subjects discontinued due to adverse events during the open-label phase.

Table 2 below summarizes subject disposition in the study.

Table 2. Subject Disposition and Subjects Analyzed

	Double-Blind Phase		Open-Label Phase	
Subjects Screened	**N=344**		**N=280**	
	Sildenafil	**Placebo**	**Previous Sildenafil**	**Previous Placebo**
Subjects treated	n=154	n=153	n=142	n=138
Intent-to-treat	147 (95.5%)	147 (96.1%)	141 (99.3%)	136 (98.6%)
Subjects completed	142 (92.2%)	138 (90.2%)	140 (98.6%)	134 (97.1%)
Total discontinued	12 (7.8%)	15 (9.8%)	2 (1.4%)	4 (2.9%)
Discontinuations related to study drug	0	1 (0.7)	0	0
Adverse events	0	1 (0.7)	0	0
Discontinuations not related to study drug	12 (7.8%)	14 (9.2%)	2 (1.4%)	4 (2.9%)
Subject defaulted	5 (3.2%)	11 (7.2%)	2 (1.4%)	3 (2.2%)
Other	5 (3.2%)	3 (2.0%)	0	1 (0.7%)
Adverse events	2 (1.3%)	0	0	0

N = number of subjects; n = number of subjects in the specified category.

In the double-blind treatment phase, demographic characteristics were similar for all subjects who took study medication and for the ITT subjects. The majority of subjects were Caucasian and >45 years of age. Table 3 below summarizes the demographic characteristics.

Table 3. Demographics

	Double-Blind Phase		Open-Label Phase	
	Sildenafil N=154	**Placebo N=153**	**Previous Sildenafil N=142**	**Previous Placebo N=138**
Age (years) n (%)				
<18	0	0	0	0
18-44	65 (42.2)	56 (36.6)	63 (44.4)	51 (37.0)
45-64	89 (57.8)	97 (63.4)	79 (55.6)	87 (63.0)
≥65	0	0	0	0
Mean (SD)	45.1 (7.8)	45.2 (8.5)	44.9 (7.6)	45.2 (8.8)
Min – Max	21-55	18-55	26-55	18-55
Race n (%)				
White	141 (91.6)	140 (91.5)	130 (91.5)	127 (92.0)
Black	4 (2.6)	4 (2.6)	3 (2.1)	3 (2.2)
Other	9 (5.8)	9 (5.9)	9 (6.3)	8 (5.8)
Height (cm)				
Mean (SD)	174.3 (7.4)	175.3 (7.5)	174.3 (7.3)	175.3 (7.6)
Weight (kg)				
Mean (SD)	80.0 (13.1)	82.8 (14.0)	79.8 (13.3)	83.1 (14.5)
Baseline diagnosis				
(Mean duration years since first diagnosis)				
Mixed	61 (2.09)	69 (1.83)	54 (2.20)	60 (1.85)
Organic	19 (3.39)	24 (4.32)	19 (3.39)	22 (4.19)
Psychogenic	74 (2.06)	60 (1.75)	69 (2.09)	56 (1.77)

Max = maximum; Min = minimum; N = number of subjects; n = number of subjects; SD = standard deviation.

Efficacy Results:

Primary Endpoint: The primary analysis from the double-blind treatment phase of the study evaluated the change from Baseline for subject's percent erection responses of Grade 3 or 4 of erection quality (hardness) to Question 5 from the event log at Week 6. The mean score of change was significantly better in the sildenafil treatment group than in the placebo treatment group ($p<0.0001$). Results for the ITT population are presented in Table 4.

Table 4. Summary of Primary Efficacy Analysis: Erection Quality (Hardness) - Change From Baseline to Week 6 (LOCF) in Subject's Percent Erection Responses of Grade 3 or 4 to 5 from the Event Log - ITT Population (Double-Blind Phase)

	N	LS Mean Change (SE)	p – Value*
Sildenafil	140	39.55 (3.13)	<0.0001
Placebo	142	10.63 (2.98)	

* The LS Mean, SE, and p-value are derived from an ANCOVA model with terms for treatment group, investigator site, baseline value of the percent of Grades 3 or 4 response of erection quality from Question 5 of event log, duration of ED, etiology of ED, subject age, and treatment by Baseline interaction ($p<0.05$).
ED = erectile dysfunction; ITT = Intent-to-Treat; LOCF = Last Observation Carried Forward; LS = least square; N = number of subjects; SE = standard error.

The efficacy analysis of the open-label treatment phase summarized results at Week 6, Week 12 (LOCF), and change from Week 6 to Week 12 (LOCF) in subject's percent erection responses of Grade 3 or 4 to Question 5 from the event log. Results for the ITT population are presented in Table 5.

Table 5. Percent Responses of Grade 3 or 4 to Question 5- ITT Population (Open-Label Phase)

	N	Baseline (Week 6) Mean (SD)	Week 12 Mean (SD)	Change (Week 6-12) Mean (SD)
Previous sildenafil	139	84.98 (27.72)	92.18 (19.7)	7.2 (22.39)
Previous placebo	134	56.07 (39.51)	93.29 (15.9)	37.22 (38.51)

ITT = Intent-to-treat; N = number of subjects; SD = standard deviation.

Secondary Endpoints:

Quality of Erection Questionnaire; Total Score: Analysis of the QEQ total score during the double-blind treatment phase summarized the changes from Baseline to Week 6 (LOCF) in QEQ total score. Results for the ITT population are presented in Table 6.

The QEQ total score was defined as the sum of 6 items (Q1 and Q3 - Q7) and was transformed into a 0-100 scale as follows:

QEQ total score = (QEQ total raw score – 6) x 100/24

Please note that QEQ Question 2 was not included in total score based on QEQ validation results. In a previous study, item analysis (unrotated factor solution) and reliability showed that Question 2 had lower final communality, factor loading, and all item total correlations than the other 6 items (Q1 and Q3 - Q7). Therefore, response to Q2 was excluded from the QEQ total scores.

Table 6. QEQ – Total Score Change From Baseline to Week 6 (LOCF) - ITT Population (Double-Blind Phase)

	N	LS Mean (SE)	p – Value*
Sildenafil	146	41.06 (2.51)	<0.0001
Placebo	143	6.85 (2.44)	

* The LS Mean, SE, and p-value are derived from an ANCOVA model with terms for treatment group, investigator site, baseline value of the transformed QEQ, duration of ED, etiology of ED, subject age, and treatment by baseline interaction ($p<0.05$).
ANCOVA = analysis of covariance; ED = erectile dysfunction; ITT = Intent-to-treat; LOCF = Last Observation Carried Forward; LS = least square; QEQ = quality of erection questionnaire; SE = standard error.

The change from Baseline in QEQ total score showed a statistically significant improvement in the sildenafil treatment group as compared to the placebo treatment group at Week 6 ($p <0.0001$).

Analysis of the QEQ total score during the open-label treatment phase summarized results at Week 6, Week 12 (LOCF), and change from Week 6 to Week 12 (LOCF) in subject's total QEQ score. Results for the ITT population are presented in Table 7.

Table 7. QEQ – Total Score Change From Baseline (Week 6) to Week 12 (LOCF) - ITT Population (Open-Label Phase)

	N	Baseline (Week 6) Mean (SD)	Week 12 Mean (SD)	Change (Week 6-12) Mean (SD)
Previous sildenafil	140	76.67 (26.47)	85.33 (20.22)	8.66 (20.57)
Previous placebo	134	45.30 (31.44)	84.45 (21.32)	39.15 (30.46)

ITT = Intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects; QEQ = Quality of Erection Questionnaire; SD = standard deviation.

Results showed improvements in QEQ total score during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Response to Individual QEQ Questions: The analyses for the individual questions of QEQ within the ITT population are presented in Table 8.

A statistically significant improvement from Baseline was observed in the response to all questions for the sildenafil treatment group as compared with the placebo group at Week 6 ($p<0.0001$).

Table 8. Summary of the Mean Change From Baseline in QEQ Q1, Q3 – Q7 – ITT Population (Double-Blind Phase) at Week 6

		N	LS Mean (SE)	p–Value*
Question 1	Sildenafil	146	1.46 (0.11)	<0.0001†
	Placebo	143	0.11 (0.11)	
Question 3	Sildenafil	146	1.79 (0.11)	<0.0001
	Placebo	143	0.28 (0.11)	
Question 4	Sildenafil	146	1.46 (0.10)	<0.0001†
	Placebo	144	0.19 (0.10)	
Question 5	Sildenafil	146	1.78 (0.12)	<0.0001
	Placebo	144	0.44 (0.11)	
Question 6	Sildenafil	146	1.66 (0.11)	<0.0001
	Placebo	144	0.34 (0.11)	
Question 7	Sildenafil	146	1.66 (0.11)	<0.0001†
	Placebo	144	0.34 (0.10)	

∗ The LS Mean, SE, and p-value are derived from an ANCOVA model with terms for treatment group, investigator site, baseline value of the transformed QEQ, duration of ED, etiology of ED, and subject age.
† p-value is based on model which also includes a term for treatment by baseline interaction.
ANCOVA = analysis of covariance; ED = erectile dysfunction; ITT = Intent to treat; LS = least square; N = number of subjects; Q = question; QEQ = quality of erection questionnaire; SE = standard error.

Analyses of the individual QEQ questions during the open-label treatment phase summarized results at Week 6, Week 12 (LOCF), and change from Week 6 to Week 12 (LOCF) in subjects' response to individual questions. Results for the ITT population are presented in Table 9.

Results showed improvements in each QEQ question during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Table 9. Summary of the Mean Change From Baseline in QEQ Q1, Q3 – Q7 – ITT Population (Open-Label Phase)

		N	Baseline (Wk 6) Mean (SD)	Wk 12 Mean (SD)	Change (Wk 6-12) Mean (SD)
Question 1	Previous sildenafil	140	4.19 (1.22)	4.55 (0.91)	0.36 (0.88)
	Previous placebo	134	2.97 (1.49)	4.53 (0.92)	1.56 (1.41)
Question 3	Previous sildenafil	140	4.03 (1.22)	4.30 (1.02)	0.27 (1.05)
	Previous placebo	134	2.69 (1.36)	4.32 (0.99)	1.63 (1.44)
Question 4	Previous sildenafil	140	4.14 (1.03)	4.40 (0.79)	0.26 (0.93)
	Previous placebo	135	2.93 (1.35)	4.37 (0.90)	1.44 (1.29)
Question 5	Previous sildenafil	140	4.00 (1.21)	4.36 (0.91)	0.36 (1.03)
	Previous placebo	135	2.76 (1.35)	4.33 (0.91)	1.57 (1.37)
Question 6	Previous sildenafil	140	4.06 (1.14)	4.46 (0.87)	0.40 (1.01)
	Previous placebo	135	2.79 (1.27)	4.34 (0.92)	1.55 (1.29)
Question 7	Previous sildenafil	140	3.99 (1.14)	4.41 (0.84)	0.43 (1.07)
	Previous placebo	135	2.73 (1.27)	4.38 (0.85)	1.65 (1.29)

ITT = intent to treat; N = number of subjects; QEQ = Quality of Erection Questionnaire; Q = question; SD = standard deviation; Wk = week.

IIEF Questions Q3 and Q4: The responses to IIEF Question 3 "How often were you able to penetrate your partner?" and IIEF Question 4 "How often were you able to maintain your

erection after penetration?" were analyzed separately. For the double-blind treatment phase, these analyses are summarized in Table 10.

A statistically significant improvement from Baseline was observed in the response to both questions for the sildenafil treatment group as compared with the placebo group at Week 6 ($p<0.0001$).

Table 10. Summary of the Mean Change From Baseline in IIEF Questions 3 and 4- ITT Population (Double-Blind Phase)

		N	LS Mean (SE)	p–Value*
Question 3	Sildenafil	146	1.30 (0.12)	<0.0001
	Placebo	144	0.12 (0.11)	
Question 4	Sildenafil	146	1.71 (0.12)	<0.0001†
	Placebo	144	0.34 (0.11)	

* The LS Mean, SE, and p-value are derived from ANCOVA model with terms for treatment group, investigator site, baseline value of the corresponding IIEF Q3 and Q4, duration of ED, etiology of ED, and subject age.
† P-value is based on model which also includes a term for treatment by baseline interaction.
ANCOVA = analysis of covariance; ED = erectile dysfunction; IIEF = International Index of Erectile Function; ITT = intent-to-treat; LS = least square; N = number of subjects; SE = standard error.

For the open-label treatment phase, analyses of IIEF Questions 3 and 4 are summarized in Table 11.

Results showed improvements in each question during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Table 11. Summary of the Mean Change From Baseline in IIEF Questions 3 and 4- ITT Population (Open-Label Phase)

		N	Baseline (Wk 6) Mean (SD)	Wk 12 Mean (SD)	Change (Wk 6-12) Mean (SD)
Question 3	Previous sildenafil	139	4.18 (1.17)	4.53 (0.92)	0.35 (1.05)
	Previous placebo	139	3.11 (1.43)	4.53 (0.89)	1.41 (1.44)
Question 4	Previous sildenafil	139	4.09 (1.20)	4.38 (1.04)	0.29 (1.03)
	Previous placebo	139	2.84 (1.42)	4.39 (1.01)	1.56 (1.43)

IIEF = International Index of Erectile Function; ITT = intent-to-treat; N = number of subjects; SD = standard deviation; Wk = week.

International Index of Erectile Function Domains: IIEF was a 15-item questionnaire. Questions 1 through 5 and question 15 of the IIEF were categorized as erectile function Domain; Questions 6 through 8 were categorized as intercourse satisfaction domain; Questions 9 and 10 were categorized as orgasmic function domain; Questions 11 and 12 were categorized as sexual desire domain; Questions 13 and 14 were categorized as overall satisfaction domain. Questions 1 through 10 were rated on a 6-point scale, with 1 representing the worst response and 5 the best. A score of 0 corresponded to lack of sexual activity, including intercourse. Questions 11 through 15 were rated on a 5-point scale, with a

score of 1 representing the worst response and 5 the best. The responses to IIEF questionnaire by domain are presented in Table 12 for the double-blind phase of the study.

A statistically significant improvement from Baseline was observed in the sildenafil treatment group as compared to the placebo treatment group for all 5 IIEF domains at the Week 6 ($p < 0.0001$).

Table 12. Summary of the Mean Change From Baseline in IIEF Domains – ITT Population (Double-Blind Phase)

		N	LS Mean (SE)	p–Value*
Erectile function	Sildenafil	148	8.68 (0.57)	<0.0001†
	Placebo	145	1.35 (0.55)	
Intercourse satisfaction	Sildenafil	145	3.92 (0.26)	<0.0001
	Placebo	144	1.30 (0.25)	
Orgasmic function	Sildenafil	146	1.58 (0.22)	<0.0001†
	Placebo	143	-0.04 (0.22)	
Overall satisfaction	Sildenafil	146	2.91 (0.21)	<0.0001†
	Placebo	144	0.45 (0.20)	
Sexual desire	Sildenafil	146	0.88 (0.13)	<0.0001
	Placebo	143	0.15 (0.13)	

* The LS Mean, SE, and p-value are derived from ANCOVA model with terms for treatment group, investigator site, baseline value of the corresponding IIEF domains, duration of ED, etiology of ED, and subject age.
† p-value is based on model which also includes a term for treatment by baseline interaction.
ANCOVA = Analysis of Covariance; ED = erectile dysfunction; IIEF = International Index of Erectile Function; ITT = intent-to-treat; LS = least square; N = number of subjects; SE = standard error.

The responses to IIEF questionnaire by domains are presented in Table 13 for the open-label phase of the study.

Results showed improvements in all IIEF domains during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Table 13. Summary of the Mean Change From Baseline in IIEF Domains – ITT Population (Open-Label Phase)

		N	Baseline (Wk 6) Mean (SD)	Wk 12 Mean (SD)	Change (Wk 6-12) Mean (SD)
Erectile	Previous sildenafil	139	24.45 (5.89)	26.35 (5.03)	1.91 (4.35)
Function	Previous placebo	135	17.62 (7.30)	26.42 (4.55)	8.80 (7.11)
Intercourse	Previous sildenafil	140	12.26 (2.51)	13.07 (2.19)	0.81 (2.31)
Satisfaction	Previous placebo	135	9.77 (3.13)	13.13 (1.94)	3.36 (3.14)
Orgasmic	Previous sildenafil	139	8.36 (2.47)	8.97 (1.74)	0.56 (1.78)
Function	Previous placebo	133	6.95 (2.73)	9.11 (1.61)	2.90 (2.49)
Overall	Previous sildenafil	139	8.12 (2.10)	8.68 (1.77)	0.56 (1.78)
Satisfaction	Previous placebo	135	5.87 (2.53)	8.75 (1.62)	2.87 (2.55)
Sexual	Previous sildenafil	140	7.78 (1.40)	8.29 (1.41)	0.51 (1.50)
Desire	Previous placebo	134	7.10 (1.50)	8.27 (1.23)	1.16 (1.52)

IIEF = International Index of Erectile Function; ITT = intent-to-treat; N = number of subjects; SD = standard deviation; Wk = week.

Self Esteem and Relationship (Questionnaire) Domains: SEAR was a 14-item questionnaire. Questions 1 through 8 of the SEAR questionnaire were categorized as sexual activity domain; Questions 9 through 14 were categorized as confidence domain; Questions 9-12 were categorized as Self-Esteem Subscale and Questions 13 and 14 were categorized as Overall Relationship Subscale. All questions were rated on a 5-point scale, with 1 representing the worst response and 5 the best. The responses to SEAR questionnaire by domain for the double-blind treatment phase are summarized and presented in Table 14.

A statistically significant improvement from Baseline was observed in the sildenafil treatment group as compared to the placebo group in all SEAR domains at Week 6 ($p<0.0001$).

Table 14. Summary of the Mean Change From Baseline in SEAR Domains – ITT Population (Double-Blind Phase)

		N	LS Mean (SE)	p–Value*
Sexual activity	Sildenafil	146	30.72 (2.02)	<0.0001
	Placebo	144	5.62 (1.97)	
Self-Esteem	Sildenafil	146	28.28 (2.06)	<0.0001
	Placebo	144	5.67 (2.02)	
Overall relationship	Sildenafil	146	22.63 (2.32)	<0.0001†
	Placebo	144	2.28 (2.27)	
Confidence	Sildenafil	146	26.42 (1.97)	<0.0001
	Placebo	144	4.56 (1.92)	

* The LS Mean, SE, and p-value are derived from ANCOVA model with terms for treatment group, investigator site, baseline value of the corresponding SEAR domains, duration of ED, etiology of ED, and subject age.
† p-value is based on model which also includes a term for treatment by baseline interaction
ANCOVA = analysis of covariance; ED = erectile dysfunction; ITT = intent-to-treat; LS = least square; N = number of subjects; SE = standard error; SEAR = Self Esteem and Relationship (Questionnaire).

The responses to SEAR questionnaire by domain for the open-label treatment phase are presented in Table 15.

Results showed improvements in all SEAR Domains during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Table 15. Summary of the Mean Change From Baseline in SEAR Domains – ITT Population (Open-Label Phase)

		N	Baseline (Wk 6) Mean (SD)	Wk 12 Mean (SD)	Change (Wk 6-12) Mean (SD)
Sexual Activity	Previous sildenafil	140	72.8 (22.84)	81.7 (19.62)	8.9 (17.89)
	Previous placebo	135	48.8 (25.52)	81.6 (17.95)	32.8 (25.97)
Self-Esteem	Previous sildenafil	140	76.4 (23.16)	83.7 (20.77)	7.3 (18.58)
	Previous placebo	135	53.4 (27.22)	82.1 (19.60)	28.7 (28.45)
Overall Relationship	Previous sildenafil	140	78.2 (25.02)	84.2 (21.18)	6.0 (21.34)
	Previous placebo	135	57.5 (30.24)	83.5 (20.18)	26.0 (28.49)
Confidence	Previous sildenafil	140	77.0 (21.56)	83.9 (19.78)	6.9 (17.41)
	Previous placebo	135	54.8 (25.27)	82.6 (18.47)	27.8 (25.52)

ITT = intent-to-treat; N = number of subjects; SD = standard deviation; SEAR = Self Esteem and Relationship (Questionnaire); Wk = Week.

Self Esteem and Relationship (SEAR) Questionnaire Total Scores: The analysis of SEAR total scores for the double-blind treatment phase are summarized in Table 16.

A statistically significant improvement from baseline was observed for the SEAR total score in the sildenafil treatment group as compared to the placebo group at Week 6 ($p < 0.0001$).

Table 16. SEAR Total Score Change From Baseline to Week 6 (LOCF) - ITT Population (Double-Blind Phase)

	N	LS Mean (SE)	p – Value*
Sildenafil	146	28.91 (1.92)	<0.0001
Placebo	144	5.19 (1.88)	

* The LS Mean, SE, and p-value are derived from ANCOVA model with terms for treatment group, investigator site, baseline value of the corresponding SEAR Total score, duration of ED, etiology of ED and subject age.
ANCOVA = analysis of covariance; ED = erectile dysfunction; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; LS = least square; N = number of subjects; SE = standard error; SEAR = Self Esteem and Relationship (Questionnaire).

The analysis of SEAR total scores for the open-label treatment phase are summarized and presented in Table 17.

Results showed improvements in SEAR total scores during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with the greatest improvement occurring in previously placebo-treated subjects.

Table 17. SEAR Total Score Change From Baseline (Week 6) to Week 12 (LOCF) - ITT Population (Open-Label Phase)

	N	Baseline (Wk 6) Mean (SD)	Wk 12 Mean (SD)	Change (Wk 6-12) Mean (SD)
Previous sildenafil	140	74.60 (21.73)	82.61 (19.02)	8.01 (16.74)
Previous placebo	135	51.35 (24.70)	82.02 (17.73)	30.67 (24.94)

ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects; SD = standard deviation; SEAR = Self Esteem and Relationship (Questionnaire); Wk = week.

Erectile Dysfunction Inventory of Treatment Satisfaction Index Score – Response: The analysis of EDITS Index scores for the double-blind treatment phase are summarized and presented in Table 18.

EDITS Index is defined as the mean raw score of EDITS Questions 1-11, multiplied by 25. Questions 1 through 11 of the EDITS were rated on a 5-point scale, with scores of 0 (worst outcome) to 4 (best outcome). An individual subject's EDITS Index score could range from 0 to 100. Results showed a significantly higher satisfaction in sildenafil treatment group as compared to the placebo group based on EDITS total scores at Week 6 ($p<0.0001$).

Table 18. EDITS Index Score: Response at Week 6 (LOCF) - ITT Population (Double-Blind Phase)

	N	LS Mean (SE)	p – Value*
Sildenafil	147	76.34 (1.81)	<0.0001
Placebo	145	52.17 (1.76)	

* The LS Mean, SE, and p-value are derived from ANCOVA model with terms for treatment group, investigator site, duration of ED, etiology of ED and subject age.
ANCOVA = Analysis of Covariance; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; LS = least square; N = number of subjects; SE = standard error.

Results showed improvements in EDITS total scores during the open-label treatment phase in both previously sildenafil-treated subjects and previously placebo-treated subjects, with no difference (Table 19).

Table 19. EDITS Index Score: Response at Week 12 - ITT Population (Open-Label Phase)

	N	Mean (SD)
Previous sildenafil	140	82.84 (14.62)
Previous placebo	135	83.00 (13.15)

EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; ITT = intent-to-treat; N = number of subjects; SD = standard deviation.

Subjects whose EDITS Index score was ≥50 were defined as "satisfied with treatment". Results showed a significantly higher percentage of satisfaction in sildenafil treatment group as compared to the placebo group at Week 6 (odds ratio = 9.26, $p<0.0001$). The estimated percentages of improvement were 90.0% and 49.2% at Week 6 for the sildenafil and placebo groups, respectively (Table 20).

Table 20. EDITS Index Score: Dichotomized Response at Week 6 - ITT Population (Double-Blind Phase)

	N	Estimated Percent*	95% CI*	Odds Ratio†	p - Value
Sildenafil	147	90.0	84.0, 93.9	9.26	<0.0001
Placebo	145	49.2	41.1, 57.4		

* Estimated percent and 95% CI computed from logistic regression, adjusting for model covariates: treatment group, baseline percent, duration of ED, etiology of ED, and subject age.

† The odds ratio provides a proportional likelihood of treatment satisfaction in one group relative to the other.

CI = confidence interval; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction. ITT = intent-to-treat; N = number of subjects.

EDITS Index score dichotomized response showed 96.4% of previously sildenafil-treated subjects and 97.8% of previously placebo-treated subjects at Week 12 satisfied with treatment (Table 21).

Table 21. EDITS Index Score: Dichotomized Response at Week 12 - ITT Population (Open-Label Phase)

	EDITS Index Score >50	EDITS Index Score ≤50
Previous sildenafil	135 (96.4)	5 (3.6)
Previous placebo	132 (97.8)	3 (2.2)

EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; ITT = intent-to-treat.

Global Efficacy Assessment (GEA) Questions: The responses to the Global Efficacy Assessment questions at the end of the double-blind treatment phase (Week 6) for the ITT population are summarized in Table 22. When asked whether treatment (relative to no treatment) had improved their erections, 88.5% of sildenafil-treated subjects and 43.1% of placebo-treated subjects answered a positive response. When asked whether treatment (relative to no treatment) had improved their ability to have sexual intercourse, 89.1% of sildenafil-treated subjects and 45.1% of placebo-treated subjects answered a positive response.

Table 22. Global Efficacy Assessment (GEA) Questions 1 and 2: Responses at Week 6 - ITT Population (Double-Blind Phase)

		N	Estimated Percent*	95% CI*	Odds Ratio†	p-Value
Medication improved erections	Sildenafil	147	88.5	82.3, 92.8	10.19	<0.0001
	Placebo	144	43.1	35.2, 51.4		
Medication improved intercourse	Sildenafil	145	89.1	82.8, 93.2	9.90	<0.0001
	Placebo	142	45.1	37.1, 53.4		

* Estimated percent and 95% CI computed from logistic regression, adjusting for model covariates: treatment group, baseline percent, duration of ED, etiology of ED, and subject age.

† The odds ratio provides a proportional likelihood of treatment satisfaction in one group relative to the other.

CI = confidence interval; ED = erectile dysfunction; GEA = Global Efficacy Assessment; ITT = intent-to-treat; N = number of subjects.

The responses to the Global Efficacy Assessment questions at the end of the open-label treatment phase (Week 12) for the ITT population are summarized in Table 23. When asked whether treatment (relative to no treatment) had improved their erections, 97.86% of previously sildenafil-treated subjects and 100% of previously placebo-treated subjects answered a positive response. When asked whether treatment (relative to no treatment) had improved their ability to have sexual intercourse, 97.14% of previously sildenafil-treated subjects and 100% of previously placebo-treated subjects answered a positive response.

Table 23. Global Efficacy Assessment (GEA) Questions 1 and 2: Responses at Week 12- ITT Population (Open-Label Phase)

		N	Subjects Who Responded Yes	Subjects Who Responded No
Medication improved erections	Previous sildenafil	140	137 (97.86)	3 (2.14)
	Previous placebo	134	134 (100)	0
Medication improved intercourse	Previous sildenafil	140	136 (97.14)	4 (2.86)
	Previous placebo	134	134 (100)	0

GEA = Global Efficacy Assessment; ITT = intent-to-treat; N = number of subjects.

Erection Quality – Hardness: The event log worksheet was used to record information on sexual intercourse. For the double-blind treatment phase, the percent of erection responses of Grades 3 or 4 to Question 5 of the Event Log is summarized in Table 24.

Significantly more sildenafil-treated subjects had a Grade 3 or 4 erection as compared with placebo-treated subjects (87.5% versus 57.1%, p <0.0001).

Table 24. Erection Quality (Hardness): Percent Erection Responses of Grade 3 or 4 to Question 5 From the Event Log at Week 6 (LOCF) - ITT Population (Double-Blind Phase)

		N	Estimated Percent*	95% CI*	Odds Ratio†	p - Value
Grade 3 or 4	Sildenafil	140	87.5	82.5, 91.2	5.26	<0.0001
	Placebo	142	57.1	50.3, 63.7		

* Estimated percent and 95% CI computed from logistic regression, adjusting for model covariates: treatment group, baseline percent, duration of ED, etiology of ED, and subject age.

† The odds ratio provides a proportional likelihood of treatment effect in one group relative to the other.

CI = confidence interval; ED = erectile dysfunction; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects.

For the double-blind treatment phase, the percent of erection responses of Grade 1, 2, 3, or 4 to Question 5 of the event log is summarized in Table 25.

Significantly less sildenafil-treated subjects had a Grade 1, 2, or 3 erection as compared with placebo-treated subjects and significantly more sildenafil-treated subjects had a Grade 4 erection as compared with placebo-treated subjects (58.2% versus 14.0%, p <0.0001).

Table 25. Erection Quality (Hardness): Percent Erection Responses of Grade 1, 2, 3, or 4 to Question 5 From the Event Log at Week 6 (LOCF) - ITT Population (Double-Blind Phase)

		N	Estimated Percent*	95% CI*	Odds Ratio†	p - Value
Grade 1	Sildenafil	140	3.2	1.9, 5.6	0.22	<0.0001
	Placebo	142	13.2	9.9, 17.3		
Grade 2	Sildenafil	140	6.7	4.8, 9.3	0.37	<0.0001
	Placebo	142	16.3	13.2, 20.1		
Grade 3	Sildenafil	140	27.8	22.7, 33.5	0.53	0.0007
	Placebo	142	41.9	36.1, 48.0		
Grade 4	Sildenafil	140	58.2	51.6, 64.5	8.53	<0.0001
	Placebo	142	14.0	10.1, 19.1		

* Estimated percent and 95% CI computed from logistic regression, adjusting for model covariates: treatment group, baseline percent, duration of ED, etiology of ED, and subject age.
† The odds ratio provides a proportional likelihood of treatment effect in one group relative to the other.
CI = confidence interval; ED = erectile dysfunction; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects.

For the open-label treatment phase, the percent of erection responses of Grade 1, 2, 3, or 4 to Question 5 of the event log is summarized in Table 26. At Week 12, the majority of previously sildenafil-treated subjects (67.5%) and the majority of previously placebo-treated subjects (60.6%) experienced Grade 4 erections. Again, these data showed that sildenafil improved erection quality in both previously sildenafil-treated subjects and previously placebo-treated subjects.

Table 26. Erection Quality (Hardness): Percent Erection Responses of Grade 1, 2, 3 or 4 to Question 5 From the Event Log at Week 12 (LOCF) - ITT Population (Open-Label Phase)

		N	Mean Percent (SD)
Grade 1	Previous sildenafil	139	0.83 (4.70)
	Previous placebo	134	1.46 (8.21)
Grade 2	Previous sildenafil	139	5.07 (13.38)
	Previous placebo	134	4.76 (11.82)
Grade 3	Previous sildenafil	139	24.71 (31.85)
	Previous placebo	134	32.65 (36.11)
Grade 4	Previous sildenafil	139	67.47 (38.64)
	Previous placebo	134	60.64 (40.27)

ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects; SD = standard deviation.

Intercourse Success Rates: For the double-blind treatment phase, the event log intercourse success rates are summarized in Table 27.

A significantly higher percentage of sildenafil-treated subjects experienced successful intercourse as compared with placebo-treated subjects (93.9% versus 81.5%, p <0.0001).

Table 27. Event Log Intercourse Success Rates at Week 6 (LOCF) - ITT Population (Double-Blind Phase)

		N	Estimated Percent	95% CI*	Odds Ratio†	p - Value
Success rate	Sildenafil	140	93.9	90.7, 96.0	3.47	<0.0001
	Placebo	142	81.5	76.6, 85.6		

* Estimated percent and 95% CI computed from logistic regression, adjusting for model covariates: treatment group, baseline, duration of ED, etiology of ED, and subject age.
† The odds ratio provides a proportional likelihood of treatment effect in one group relative to the other.
CI = confidence interval; ED = erectile dysfunction; ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects.

For the open-label treatment phase, the event log intercourse success rates are summarized in Table 28.

At Week 12, 95.5% of previously sildenafil-treated subjects and 93.2% of previously placebo-treated subjects experienced successful intercourse.

Table 28. Event Log Intercourse Success Rates at Week 12 (LOCF) - ITT Population (Open-Label Phase)

		N	Mean (SD)
Success rate	Previous sildenafil	139	95.49 (13.54)
	Previous placebo	134	93.16 (14.78)

ITT = intent-to-treat; LOCF = Last Observation Carried Forward; N = number of subjects; SD = standard deviation.

Safety Results:

Duration of Exposure to Study Drug: Duration of exposure to study drugs is summarized in Table 29.

For the double-blind phase, the median duration of treatment for the study was 42 days in both the sildenafil and placebo treatment groups and the majority of subjects had > 29 days of treatment. The median of doses taken was 20 in the sildenafil group and 16 in the placebo group.

For the open-label phase, the median duration of treatment for the study was 42 days in both the previous sildenafil and previous placebo treatment groups and the majority of subjects had > 29 days of treatment. The median of doses taken was 23.5 in the previous sildenafil group and 25 in the previous placebo group.

Table 29. Summary Treatment Duration and Average Number of Doses Taken

Duration of Treatment (Days)	Double-Blind Phase		Open-Label Phase	
	Sildenafil N=154	Placebo N=153	Previous Sildenafil N=142	Previous Placebo N=138
≤1	0	0	0	0
2-7	1	0	0	0
8-14	2	4	0	1
15-28	4	3	1	5
29-60	146	146	140	132
61-90	1	0	1	0
≥91	0	0	0	0
Median duration (days)	42.0	42.0	42.0	42.0
Range (Day)	4-88	8-56	28-68	11-58
Number of doses taken				
1	6	6	1	2
2-30	123	137	96	94
31-50	25	10	45	41
51-70	0	0	0	1
71-90	0	0	0	0
≥91	0	0	0	0
Average doses/month	7.3	6.1	16.6	17.1
Median of doses	20.0	16.0	23.5	25.0
Dose range	1-43	1-41	1-42	1-51

N = number of subjects.

Overview of Adverse Events: An overall summary of treatment-emergent adverse events (all causalities) is provided in Table 30 and Table 31 for the double-blind and open-label phase, respectively. During the double-blind treatment phase, 29 (18.8%) sildenafil-treated subjects and 17 (11.1%) placebo-treated subjects reported 38 and 23 all-causality treatment-emergent adverse events, respectively, of which 27 and 11 were considered to be treatment-related, respectively. All of the adverse events were mild or moderate in intensity. No subject had an adverse event that was rated severe.

Table 30. Summary of Treatment-Emergent Adverse Events (Double-Blind Phase)

	Sildenafil	Placebo
Number of subjects treated	154	153
Number of subjects with at least 1 adverse event	29 (18.8)	17 (11.1)
Number of adverse events	38	23
Number of subjects with at least 1 treatment-related adverse Event	19 (12.3)	9 (5.9)
Number of treatment-related adverse events	27	11
Number of subjects with serious adverse events	1 (0.6)	0
Number of subjects with treatment-related serious adverse events	0	0
Number of subjects with at least 1 severe adverse event	0	0
Number of subjects with at least 1 treatment-related severe adverse event	0	0
Number of subjects discontinued due to adverse events	2 (1.3)	1 (0.7)
Number of subjects discontinued due to treatment-related adverse events	0	1 (0.7)
Number of subjects with dose reduced or temporarily discontinued due to adverse events	3 (1.9)	1 (0.7)
Number of subjects with dose reduced or temporarily discontinued due to treatment-related adverse events	3 (1.9)	0

During the open-label treatment phase, 14 (9.9%) previously sildenafil-treated subjects and 17 (12.3%) previously placebo-treated subjects reported 26 and 25 all-causality treatment-emergent adverse events, respectively, of which 19 and 18 were considered to be treatment-related, respectively. All of the adverse events were mild or moderate in intensity. No subject had an adverse event that was rated severe.

Table 31. Summary of Treatment-Emergent Adverse Events (Open-Label Phase)

	Previous Sildenafil	Previous Placebo
Number of subjects treated	142	138
Number of subjects with at least 1 adverse event	14 (9.9)	17 (12.3)
Number of adverse events	26	25
Number of subjects with at least 1 treatment-related adverse event	10 (7.0)	13 (9.4)
Number of treatment-related adverse events	19	18
Number of subjects with serious adverse events	0	0
Number of subjects with treatment-related serious adverse events	0	0
Number of subjects with at least 1 severe adverse event	0	0
Number of subjects with at least 1 treatment-related severe adverse event	0	0
Number of subjects discontinued due to adverse events	0	0
Number of subjects discontinued due to treatment-related adverse events	0	0
Number of subjects with dose reduced or temporarily discontinued due to adverse events	2 (1.4)	2 (1.4)
Number of subjects with dose reduced or temporarily discontinued due to treatment-related adverse events	1 (0.7)	1 (0.7)

Treatment Emergent All-Causality Adverse Events: The most common treatment-emergent all-causality adverse event during the double-blind phase with an incidence of ≥2% (Table 32) was headache in 12 (7.8%) sildenafil-treated subjects and 5 (3.3%) placebo-treated subjects. Vasodilatation occurred in 4 (2.6%) sildenafil-treated subjects. The majority of these events were mild.

Table 32. Summary of All-Causality Treatment-Emergent Adverse Events (Incidence ≥2%) During the Double-Blind Phase

Body System and MedDRA Preferred Term	Sildenafil N=154	Placebo N=153
Body as a whole		
Headache	12 (7.8)	5 (3.3)
Cardiovascular		
Vasodilatation	4 (2.6)	0

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

The most common treatment-emergent all-causality adverse event during the open-label phase with an incidence of ≥2% (Table 33) was headache in 5 (3.5%) previously sildenafil-treated subjects and 7 (5.1%) previously placebo-treated subjects. Vasodilatation occurred in 4 (2.8%) previously sildenafil-treated subjects and 6 (4.3%) previously placebo treated subjects. Rhinitis occurred in 3 (2.1%) previously sildenafil-treated subjects and 2 (1.4%) previously placebo-treated subjects. The majority of these events were mild.

Table 33. Summary of All-Causality Treatment-Emergent Adverse Events (Incidence ≥ 2%) During the Open-Label Phase

Body System and MedDRA Preferred Term	Sildenafil N=142	Placebo N=138
Body as a whole		
Headache	5 (3.5)	7 (5.1)
Cardiovascular		
Vasodilatation	4 (2.8)	6 (4.3)
Respiratory		
Rhinitis	3 (2.1)	2 (1.4)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

Treatment Related Adverse Events: The most common treatment-related adverse event during the double-blind phase with an incidence of ≥2% (Table 34) was headache in 11 (7.1%) sildenafil-treated subjects and 4 (2.6%) placebo-treated subjects. Vasodilatation occurred in 4 (2.6%) sildenafil-treated subjects. The majority of these events were mild.

Table 34. Summary of Treatment-Related Treatment-Emergent Adverse Events (Incidence ≥ 2%) During the Double-Blind Phase

Body System and MedDRA Preferred Term	Sildenafil N=154	Placebo N=153
Body as a Whole		
Headache	11 (7.1)	4 (2.6)
Cardiovascular		
Vasodilatation	4 (2.6)	0

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

The most common treatment-related adverse event during the open-label phase with an incidence of ≥2% (Table 35) was headache in 5 (3.5%) previously sildenafil-treated subjects and 7 (5.1%) previously placebo-treated subjects. Vasodilatation occurred in 4 (2.8%) previously sildenafil-treated subjects and 6 (4.3%) previously placebo-treated subjects.

Rhinitis occurred in 3 (2.1%) previously sildenafil-treated subjects and 2 (1.4%) previously placebo-treated subjects. The majority of these events were mild.

Table 35. Summary of Treatment-Related Treatment-Emergent Adverse Events (Incidence ≥ 2%) During the Open-Label Phase

Body System and COSTART Preferred Term	Sildenafil N=142	Placebo N=138
Body as a whole		
Headache	5 (3.5)	7 (5.1)
Cardiovascular		
Vasodilatation	4 (2.8)	6 (4.3)
Respiratory		
Rhinitis	3 (2.1)	2 (1.4)

COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms; N = number of subjects.

Permanent Discontinuations due to Adverse Events: Three (3) subjects (two sildenafil-treated and 1 placebo-treated) discontinued from the study due to an adverse event during the double-blind phase of the study. One (0.7%) placebo-treated subject was discontinued from the study due to an adverse event (syncope); the event was considered to be treatment-related. There were no permanent discontinuations due to adverse events during the open-label phase of the study.

Dose Reductions or Temporary Discontinuations due to Adverse Events: During the double-blind phase of the study, 3 (1.9%) sildenafil-treated subjects had their dose reduced due to treatment related adverse events (headaches and dyspepsia). One (0.7%) placebo-treated subject was temporarily discontinued due to a non-treatment related adverse event.

During the open-label phase of the study, 2 (1.4%) previously sildenafil-treated subjects had their drug reduced/temporarily discontinued due to adverse events; 1 had his drug reduced due to a treatment related adverse events (headache, vasodilatation and rhinitis). Two (1.4%) previously placebo-treated subjects had their drug reduced/temporarily discontinued due to adverse events; 1 had his drug reduced due to a treatment related adverse events (headache and vasodilatation).

Serious Adverse Events (SAEs): One subject had a SAE. This SAE was considered to be unrelated to study medication.

Deaths: There were no deaths reported in the study.

Laboratory Evaluations: No laboratory data were collected in this study. No median change was observed in vital sign measurements from Baseline to the last observation during either the double-blind phase or the open-label phase of the study.

CONCLUSIONS: The purpose of this study was to evaluate the effect that sildenafil citrate has on the hardness of erections in males with ED, based on subject responses to Question 5 on the event log (hardness of erection) as measured at the end of double-blind treatment

(Week 6), and to correlate the effect that hardness of erection has on treatment satisfaction and quality of life.

This study demonstrated that sildenafil therapy statistically significantly improved hardness of erection, which was hard enough for penetration ($p < 0.0001$). In addition, sildenafil therapy demonstrated significant improvement ($p < 0.0001$) in erection penetration, erection keep, time to erection, erection time, erection hardness, and erection quality. Through QEQ item analysis, past studies have suggested that hardness of erection may be the key driver for overall satisfaction.

This study showed that sildenafil citrate is well tolerated. The majority of adverse events were mild or moderate in severity and consistent with previous trials, headache and vasodilatation were the most common treatment-related adverse events.