PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00245258

PROTOCOL NO.: A1481239

PROTOCOL TITLE: A Multicenter, Double-Blind Placebo Controlled, Fixed Dose Study With An Open-Label, Flexible Dose Phase To Assess The Efficacy Of Sildenafil Citrate In Providing A Better Sexual Experience Including Quality Of Erections And Satisfaction In Men With Erectile Dysfunction

Study Center(s): Nineteen (19) centers in the Republic of Korea (6), the Russia Federation (5), Spain (4) and Sweden (4).

Study Initiation and Completion Dates: 16 September 2005 to 01 September 2006

Phase of Development: 4

Study Objective(s):

*Primary***:** To evaluate the effect of sildenafil citrate versus placebo in males with erectile dysfunction (ED), based on subject responses to the International Index of Erectile Function – Erectile Function (IIEF-EF) domain as measured at the end of double-blind (DB) treatment (Week 8).

Secondary: to assess the relationship between treatment with sildenafil citrate or placebo and responses to the Quality of Erection Questionnaire (QEQ) and Sexual Experience Questionnaire (SEX-Q). This study also assessed efficacy, treatment satisfaction and quality of life changes in men with ED, based on the subject responses to the following assessments as measured at the end of DB treatment (Week 8) and at the end of open-label (OL) treatment (Week 12):

- Responses to the QEQ;
- Responses to the SEX-Q;
- Responses to IIEF domains for erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction;
- Event Log success rate variables;

- Responses to the Self Esteem and Relationship (SEAR) Questionnaire, including individual scores for the confidence domain (which includes the sub-domains of self esteem and overall relationship) and the sexual relationship domain;
- Responses to Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questionnaire;
- Responses to the Global Efficacy Assessment Questionnaire (GEAQ).

Safety and tolerability, based on adverse events (AEs) was also assessed.

METHODS

Study Design: This was a parallel group, multicenter study with a DB, randomized, placebo-controlled fixed dose phase followed by OL, flexible dose phase. The study involved six clinic visits over a period of 14 weeks that included a two-week screening phase, an eight-week DB treatment phase with sildenafil citrate or placebo, and a four-week OL treatment phase with sildenafil citrate. The maximum exposure to the study drug for an individual subject was to be 12 weeks.

Number of Subjects (Planned and Analyzed):

Planned: Based on a 20% screen failure rate, 312 subjects were screened to enroll the planned 250 randomized subjects. Assuming an estimated 85% evaluable rate, this would yield the required sample size of 210 evaluable subjects (70 per treatment group).

Analyzed: 288 subjects were randomized into the DB phase (94 sildenafil 50 mg, 99 sildenafil 100 mg, 95 placebo). A total of 281 subjects were evaluable for efficacy.

Diagnosis and Main Criteria for Inclusion: Male subjects aged 18 to 65 years with a documented clinical diagnosis of ED confirmed by an IIEF-EF domain score of ≤ 25. Subjects were to have had no intention of changing sexual partner for the duration of the study. Subjects prescribed, taking and/or likely to be treated with nitrates, nitric oxide donors or alpha blocker medications or who were taking or using any other commercially available drug or non-drug treatments for ED were excluded from entering the study.

Study Treatment: Sildenafil citrate 50mg or 100 mg or matched placebos. Study medication was to be taken on an outpatient basis. Each subject was dispensed two bottles (Bottles A and B) at Visits 2 and 3 (Baseline and Week 2) during the DB phase and one bottle at Visits 4 and 5 (Weeks 8 and 10) during the OL phase. For the DB treatment phase, subjects were instructed to take one tablet from Bottle A and one tablet from Bottle B prior to sexual activity, but not to take more than one tablet from each bottle per day. For the OL treatment phase, subjects were instructed to take one tablet when required for sexual activity but not more than once daily. The medication was to be swallowed with a glass of water 30-60 minutes prior to anticipated sexual activity. The subjects were also informed that sexual stimulation was required to obtain an erection, and that sexual activity was to be attempted at least twice per week.

Efficacy Evaluations:

Primary: Change in IIEF-EF scores from Baseline to Visit 4 (Week 8).

Secondary: Change from Baseline to Visit 4 (Week 8) in:

- IIEF orgasmic function, sexual desire intercourse satisfaction and overall satisfaction domains and in the IIEF individual questions;
- SEX-Q total, domain scores and individual questions;
- QEQ total score and individual questions;
- SEAR domains and sub-domains score.

EDITS total score and GEAQ responses at Visit 4 (Week 8) and Visit 6 (Week 12).

Safety Evaluations: Safety was assessed by the recording of adverse events (AEs).

Statistical Methods: Two study populations were defined. The safety set included all subjects who took at least one dose of study drug. Safety analysis was based on a safety set that was defined for the DB phase and separately for the OL phase. The full analysis set included all subjects who took at least one dose of study drug and had at least one post-Baseline efficacy evaluation.

Analysis of the primary endpoint was performed using analysis of covariance (ANCOVA) which included terms for Baseline, center, treatment group, age, ED etiology and ED duration. No interaction terms were considered.

The treatment effect was tested at the 5% significance level separately for each of the two primary comparisons (sildenafil 100 mg versus placebo and sildenafil 50 mg versus placebo). A step-down procedure was to be followed in which comparison of sildenafil 100 mg versus sildenafil 50 mg for the change in IIEF-EF domain score was carried out only when the two primary paired comparisons were both statistically significant in favor of sildenafil. No adjustment for p-value was required since the claim for overall efficacy was to be made only when both tests were statistically significant.

Secondary endpoints were analyzed using logistic regression (event log data, GEAQ questions 1 and 2), Pearson product-moment correlation coefficients (changes from Baseline between SEX-Q scores and QEQ total score with other ED efficacy parameters), descriptive statistics (OL data, safety data) or the ANCOVA model described above (all other secondary endpoints). The ANCOVA and logistic regression analyses assessed the overall treatment difference as well as three paired comparisons between treatment groups.

No inferential statistics were performed for the OL phase (Weeks 8 to 12); data was reported using descriptive statistics.

Safety data was summarized using Medical Dictionary for Regulatory Affairs Version 10.0 for each treatment group. Because a lag time of seven days was used for sildenafil studies, safety data recorded after the date of last dose of study medication but within seven days of the last dose, were treated as if they occurred during the treatment period. Safety data

recorded more than seven days after the last dose date was listed but did not otherwise contribute to safety summaries.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S1.

Table S1 Disposition of Subjects

	Sildenafil 100 mg n (%)	Sildenafil 50 mg n (%)	Placebo n (%)
Screened		319	
Assigned to DB treatment		288	
Treated	99 (100.0)	94 (100.0)	95 (100.0)
Completed DB phase	98 (99.0)	91 (96.8)	90 (94.7)
Discontinued DB treatment	1 (1.0)	3 (3.2)	5 (5.3)
Adverse event	1 (1.0)	0	1 (1.0)
Subjects defaulted[1]	0	1 (1.1)	4 (4.2)
Other[2]	0	2 (2.1)	0
Assigned to OL treatment		279	
Treated	98 (100.0)	91 (100.0)	90 (100.0)
Completed OL phase	98 (100.0)	90 (98.9)	89 (98.9)
Discontinued OL treatment	0	1 (1.1)	1 (1.1)
Adverse event	0	1 (1.1)	0
Subject defaulted[1]	0	0	1 (1.1)

1. 'Subject defaulted' includes subjects lost to follow-up and subjects no longer willing to participate.
2. 'Other' includes protocol violations, subjects who did not meet entrance criteria, and other reasons.

DB: Double-blind; OL: Open-label.

A summary of subject demographic data at entry into the DB phase is presented in Table S2, below.

Table S2 Demographic Characteristics, Double-Blind Phase (Safety Population)

Baseline Characteristics	Sildenafil 100 mg (N=99)	Sildenafil 50 mg (N=94)	Placebo (N=95)
Age (years)			
Mean (standard deviation)	51.1 (9.9)	51.8 (9.9)	49.6 (9.7)
Range	22-65	28-65	20-65
Race, n (%)			
White	63 (63.6)	59 (62.8)	62 (65.3)
Asian	35 (35.4)	35 (37.2)	33 (34.7)
Other	1 (1.0)	0	0
Duration of erectile dysfunction (years)			
Mean	3.27	3.19	3.18
Range	0.04 – 19.03	0.00 – 26.18	0.00 – 29.21

The demographic characteristics for the OL phase were similar to the DB phase.

Efficacy Results:

*Primary***:** Results of the primary efficacy analysis, the change from Baseline to Week 8 in the IIEF-EF domain, are presented in Table S3.

Table S3 Summary of Primary Efficacy Analysis: Change from Baseline in the International Index of Erectile Function – Erectile Function Domain Score (Week 8, Double-Blind Phase, Full Analysis Set)

	Baseline Mean	Change from Baseline		p-values	
		Mean (SD)	LS mean (SE)	Relative to Placebo	Relative to Sildenafil 50 mg
Sildenafil, 100 mg (N=98)	16.3	8.8 (6.35)	9.1 (0.64)	<0.0001	0.0822
Sildenafil, 50 mg (N=93)	14.9	7.9 (7.07)	7.7 (0.65)	<0.0001	
Placebo (N=90)	15.9	2.1 (5.11)	2.1 (0.66)		

LS: least squares; SD: standard deviation; SE: standard error of least squares mean.
LS Mean, SE and p-values are derived from ANCOVA model with terms for treatment group, center, Baseline value, duration of erectile dysfunction, etiology of erectile dysfunction and subject age.

Secondary: The two sildenafil groups (50 and 100 mg) were statistically significantly different compared with placebo for all the ED tools utilized in this study. All IIEF domain scores, the change from Baseline in SEX-Q total and domain scores, QEQ score, SEAR domains and sub-domains scores, EDITS total and dichotomized scores, GEAQ scores were significantly different in the sildenafil 50 mg and 100 mg groups compared with the placebo group ($p<0.0005$ for all except the sexual desire domain of IIEF for sildenafil 50 mg versus placebo, where $p=0.0116$).

The 100 mg sildenafil group showed statistically significant higher SEX-Q total and domain scores, SEAR total and the domains of sexual relationship and overall relationship, EDITS total score and GEAQ Question 3 and change from Baseline in IIEF overall satisfaction compared with the sildenafil 50 mg group ($p<0.05$). No statistically significant difference between the two sildenafil groups was seen for any of the other efficacy assessments.

Analysis of the Event Logs showed sildenafil 100 mg and sildenafil 50 mg produced statistically significant improvements compared with placebo ($p<0.05$) for the following parameters:

- Percent of occasions with sexual stimulation when an erection of Grade 1, 2 or 4 was achieved;
- Percent of occasions with sexual stimulation when an erection of Grades 3 or 4 was achieved;
- Percent of occasions with sexual stimulation when sexual intercourse was attempted;
- Percent of attempts at sexual intercourse with sexual stimulation when the erection lasted long enough for sexual intercourse;
- Percent of total attempts at intercourse within 24-hours of taking the medication when second erection was achieved;
- Percent of second erections within 24-hours of taking the medication that sexual intercourse was attempted.

Sildenafil 100 mg, but not sildenafil 50 mg, produced statistically significant improvements compared with placebo ($p<0.05$) for the following parameters:

- Percent of attempts at sexual intercourse with sexual stimulation when ejaculation or orgasm was achieved;
- Percent of total attempts at intercourse within 24-hours of taking the medication when second erection lasted long enough for successful intercourse to be achieved.

No significant difference between sildenafil 100 mg and sildenafil 50 mg were observed for any of the Event Log parameters, although a greater percentage of subjects who received the 100 mg dose had Grade 3 (42.4%) or Grade 4 (2.3%) erections when compared with the 50 mg dose (24.7% and 1.2%, respectively).

The analysis of the anxiety parameters of Event Log indicated that both sildenafil groups reported statistically significant differences compared with the placebo group for 'no anxiety about next attempt at sexual intercourse' (odds ratios of 5.99 and 2.95 for the 100 mg versus placebo and 50 mg versus placebo comparisons, respectively; $p<0.005$) and also for 'highly anxious about next attempt at sexual intercourse' (odds ratios of 0.10 and 0.15, respectively; $p<0.0001$). There was a statistically significant difference between sildenafil 50 mg and placebo for 'slight anxiety about next attempt at sexual intercourse' ($p=0.04$). 'Moderate anxiety about next attempt at sexual intercourse' was significantly different between the sildenafil 100 mg and placebo groups ($p=0.0217$). The analysis showed that 2% of subjects in the sildenafil 100 mg group, 3% of subjects in the sildenafil 50 mg group and 17.3% of subjects in the placebo group indicated that they were 'highly anxious about next attempt at sexual intercourse.'

The observations for the OL phase for all ED efficacy parameters, in general, continued to show improvement, both in the previous sildenafil groups and in the previous placebo group. The previous sildenafil 50 mg group appeared to have improved more than the previous sildenafil 100 mg group from Week 8 to Week 12. In addition, the subjects that were previously in the placebo group exhibited a greater improvement in the scores after Week 8, when they commenced treatment with sildenafil treatment, compared with subjects that had received sildenafil over the duration of the study. Most of the improvement from Baseline to Week 12 in the previous placebo group was attributed to improvement during the OL phase. At Week 12 all ED parameters for subjects in all three treatment groups appeared to have improved to similar extent.

Strong correlations were seen for the change from Baseline between the IIEF domains for erectile function, intercourse satisfaction and overall satisfaction with QEQ total score, SEX Q total score and all SEX-Q domain scores with the exception of intercourse satisfaction and the SEX-Q relationship domain which showed a moderate correlation. The IIEF domain for orgasmic function showed moderate correlations with the QEQ total score and with all SEX-Q scores.

Except for a moderate correlation between the change from Baseline for the SEAR self esteem domain and QEQ total score, strong correlations were seen in the change from

Baseline between the QEQ total score and all SEX-Q scores and the SEAR domains and subdomains, EDITS total score and GEAQ Question 3.

For the event log data moderate correlations were seen in the change from Baseline between Grade 4 erections and the QEQ total score and all SEX-Q scores and between Grade 3 or 4 erections and the SEX-Q domains for relationship and satisfaction. Changes from Baseline in Grade 3 or 4 erections were strongly correlated with the QEQ total score, the SEX-Q total score and the SEX-Q erection domain. The only other correlation of note was a moderately negative correlation between changes from Baseline between Grade 1 erection and QEQ total score, although the percent of successful attempts at intercourse approached moderate correlation levels with SEX-Q total score and the SEX-Q erection domain.

Safety Results: An overview of AEs reported during the study is presented in Table S4.

Table S4 Overview of Treatment-Emergent Adverse Events (Safety Population)

	Double-Blind Phase			Open-Label Phase		
n (%)	Sildenafil 100 mg (n=99)	Sildenafil 50 mg (N=94)	Placebo (N=95)	Previous Sildenafil 100 mg (N=98)	Previous Sildenafil 50 mg (N=91)	Previous Placebo (N=90)
Subjects with AEs	18 (18.2)	14 (14.9)	11 (11.6)	8 (8.2)	14 (15.4)	16 (17.8)
Subjects with treatment related AEs	16 (16.2)	11 (11.7)	2 (2.1)	8 (8.2)	11 (12.1)	16 (17.8)
Subjects permanently discontinued due to an AE	1 (1.0)	0	1 (1.1)	0	1 (1.1)	0
Subjects temporarily discontinued due to an AE	0	0	0	0	1 (1.1)	0
Subjects with SAEs	0	0	1 (1.1)	0	0	0
Subjects with treatment related SAEs	0	0	0	0	0	0
Subjects who died	0	0	0	0	0	0

AE: Adverse event; SAE: Serious adverse event

AEs reported in 2% or more of subjects in any treatment group during the DB phase are presented in Table S5.

Table S5 Treatment-Emergent (All Causality) Adverse Events that Occurred in >2% of Subjects in Any Treatment Group (Double-Blind Phase, Safety Set)

Preferred Term n (%)	Sildenafil 100 mg (N=99)	Sildenafil 50 mg (N=94)	Placebo (N=95)
Flushing	5 (5.1)	5 (5.3)	0
Headache	3 (3.0)	1 (1.1)	3 (3.2)
Nasal congestion	3 (3.0)	2 (2.1)	0
Dyspepsia	3 (3.0)	1 (1.1)	0

There were no deaths reported during this study.

There were two discontinuations from treatment due to AEs in the DB phase. One subject in the sildenafil 100 mg had moderate dyspepsia which was considered by the investigator to be treatment related and one subject in the placebo group had a moderate joint sprain which was not considered by the investigator to be related to treatment.

The only serious AE (SAE) reported during the DB phase was in one subject in the placebo group who experienced chest pain. The event was not considered by the investigator to be treatment-related.

AEs reported during the OL phase of the study are presented in Table S6, below.

Table S6 Treatment-Emergent (All Causality) Adverse Events that Occurred in >2% of Subjects in Any Treatment Group (Open Label Phase, Safety Set)

Preferred Term n (%)	Previous Sildenafil 100 mg (N=98)	Previous Sildenafil 50 mg (N=91)	Previous Placebo (N=90)
Flushing	6 (6.1)	5 (5.5)	3 (3.3)
Nasal congestion	1 (1.0)	1 (1.1)	6 (6.7)
Headache	0	3 (3.3)	4 (4.4)
Feeling hot	1 (1.1)	1 (1.1)	2 (2.2)
Dyspepsia	0	0	3 (3.3)

There were no deaths or serious AEs reported during the OL phase of this study. One subject permanently discontinued OL therapy. This subject had mild coronary artery stenosis which was not considered by the investigator to be related to study treatment.

CONCLUSIONS: The results of the study showed that PRN sildenafil citrate (50 mg and 100 mg) was safe and effective in the treatment of ED.

The analysis of the primary efficacy parameter, change in the score of the IIEF- EF domain at the end of eight-weeks PRN treatment with sildenafil 100 mg or sildenafil 50 mg, showed statistically significantly greater improvement compared with placebo.

The analysis of secondary efficacy parameters also showed statistically significantly greater improvements with sildenafil (100 mg or 50 mg) compared with placebo for changes from baseline to week 8 in IIEF domains, SEX-Q domains, QEQ total score, SEAR domains and subdomains. Subjects treated with sildenafil had higher observed values at week 8 compared with placebo for EDITS total score, treatment satisfaction (dichotomized EDITS scores), GEAQ and Event Log parameters (except for Grade 3 erections in both the sildenafil 50 mg and 100 mg groups, achievement of ejaculation or orgasm in the sildenafil 50 mg group, slight anxiety about next attempt in the sildenafil 100 mg group, and moderate anxiety about the next attempt in the sildenafil 50 mg group).

During the four-week OL phase, subjects previously receiving sildenafil treatment during the DB phase, continued to maintain improvement of their ED. Subjects who were on placebo treatment during the DB phase were able to achieve control of their ED within the four-week OL treatment and achieve ED control similar to subjects that had been on the sildenafil treatment throughout the study.

The SEX-Q domains and QEQ total score were either strongly or moderately correlated to the majority of the ED parameters tested. The few exceptions were: the IIEF domain for sexual desire, and Event Log parameters for successful attempts at intercourse and quality of erections that were graded 1, 2 and 3.

The treatment regimen examined during this trial, sildenafil doses of 100 mg and 50 mg, were generally safe and well tolerated. Most of the AEs were of mild severity. There were no deaths in this study and only one subject was permanently discontinued from the study due to a treatment related AE. This was an event of dyspepsia reported during the DB phase in a subject who was receiving sildenafil 100 mg. The only SAE reported (chest pain) occurred in the placebo group during the DB phase.