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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: see USPI

NCT NO.: 00249730

PROTOCOL NO.: A1481237

PROTOCOL TITLE: A prospective multicentre, parallel group study with a single blind phase and a double blind randomised phase, to evaluate the efficacy and satisfaction of Viagra® (sildenafil citrate) high dose (100 mg) titration compared with 50 mg dose, in men with erectile dysfunction.

Study Centers: This was a multicenter study conducted in Canada (5), France (3), Greece (3), Israel (3), Italy (6), Russian Federation (3), Spain (9) and the United Kingdom (10).

Study Initiation and Completion Dates: 25 October 2005 – 07 July 2006

Phase of Development: Phase 4

Study Objective(s):

Primary Objective: To compare the efficacy of Viagra® dose titration to 100 mg versus 50 mg in men with erectile dysfunction (ED), based on responses to the International Index of Erectile Function (IIEF) questionnaire, focusing on the Erectile Function (EF) domain, as measured at the beginning and at the end of the double blind treatment phase

Secondary Objective: To assess the safety and tolerability as well as treatment satisfaction in these 2 groups of men

METHODS

Study Design: This was a multicenter study conducted in men with ED. There were 2 phases: a single-blind phase when all subjects received sildenafil 50 mg + placebo (100 mg) for 4 weeks followed by a double-blind randomized phase when subjects received either sildenafil 50 mg + placebo (100 mg) or sildenafil 100 mg + placebo (50 mg) for 4 weeks. Subjects took the study treatment as required, but not more than once daily. Subjects were blinded to treatment during both phases of the study; investigators were blinded to treatment during the double-blind randomized phase only.

Subjects visited the center on 4 occasions: a screening visit (Visit 1), a baseline visit (Visit 2) 2 weeks after Visit 1, a randomization visit (Visit 3) 4 weeks after Visit 2 and an end of study visit (Visit 4) 4 weeks after Visit 3. Subjects were encouraged to attempt sexual intercourse on a minimum of 4 occasions between visits. All subjects were given sildenafil 50 mg + placebo at Visit 2 and reminded that medication should be taken as necessary and no more than once daily. At Visit 3, subjects were randomized to received sildenafil 100 mg + placebo (titrated dose group) or sildenafil 50 mg + placebo (fixed dose group) for the next 4 weeks. Efficacy and safety assessments were conducted.

Number of Subjects (Planned and Analyzed):

Planned: It was planned to enroll approximately 500 subjects (250 subjects in each treatment group).

Analyzed: A total of 492 subjects were treated during the single blind phase of the study and a total of 477 subjects were randomized to the double blind phase of the study. Of these, 240 were randomized to sildenafil 50 mg + placebo and 237 were randomized to sildenafil 100 mg + placebo. One subject in each treatment arm was randomized but not treated.

Diagnosis and Main Criteria for Inclusion: This study enrolled male subjects who had been clinically diagnosed with ED using the IIEF-EF domain (score ≤ 25). Subjects were aged ≥ 18 years and had to have been in a stable relationship with the same partner for at least 6 months and be willing to attempt sexual intercourse.

Study Treatment: Sildenafil and matching placebo tablets were provided by the sponsor. Subjects were given 2 bottles of blinded medication containing 28 tablets of either study drug or matching placebo. Subjects swallowed 2 tablets (1 from each bottle) as required, not more than once daily. All medication was taken orally with a glass of water approximately 1 hour (between 30 minutes and 4 hours) before sexual activity.

Efficacy Evaluations: At each visit, subjects completed the IIEF questionnaire. Subjects also completed a subject event log diary every time they took study drug, a Quality of Erection Questionnaire (QEQ) at Visits 2, 3 and 4, Global Efficacy Questions at Visit 4 or early termination, a Sexual Experience Questionnaire (SEX-Q) at Visits 2, 3 and 4, an Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) at Visits 3 and 4.

Safety Evaluations: At each visit, observed or volunteered adverse events (AEs) regardless of treatment group or suspected causal relationship to study drug were recorded on the AE page(s) of the case report form. Blood pressure and pulse rate measurements were also taken at each visit.

Statistical Methods:

Two study populations were analyzed for efficacy:

- The Full Analysis Set (FAS) population included all subjects who were randomized at Visit 3 and completed at least one post randomization efficacy assessment.

- The Per Protocol (PP) population included all subjects in the FAS population who also fulfilled the following criteria: no major violation of the inclusion/exclusion criteria; no major protocol violations and did not withdraw prematurely from the study, or had IIEF efficacy assessments at randomization and end of study within the pre-defined visit windows.

Efficacy: The difference between treatment arms was assessed by looking at the change in IIEF-EF domain scores between Visits 3 (randomization to double-blind treatment) and 4 (end of treatment). The IIEF-EF domain score was calculated as the sum of questions 1 to 5 and question 15 of the IIEF.

This was analyzed using an analysis of covariance (ANCOVA) for the full analysis set (FAS) and per protocol (PP) populations, including terms to account for score at randomization, country and treatment arm. For subjects who discontinued prior to Visit 4, a last observation carried forward (LOCF) approach was used for the FAS. The comparison of interest was sildenafil 50 mg to 100 mg titrated dose versus sildenafil 50 mg fixed dose. The mean difference of the titrated group compared to the fixed dose group was calculated with 95% confidence intervals for these differences. Summary statistics (n, mean, standard deviation, median, minimum and maximum) at each visit, excluding screening, are also presented along with plots of unadjusted mean change in scores. Secondary endpoints were analyzed using an ANCOVA, logistic regression or summary statistics.

Safety: Safety data were reported using the Pfizer Data Standards.

RESULTS

Subject Disposition and Demography: A total of 560 subjects were screened and 492 subjects were assigned to treatment and received sildenafil 50 mg + placebo during the single blind phase of the study. Of these, 476 (96.7%) subjects completed this phase of the study and 16 (3.3%) subjects discontinued for reasons summarized in Table S1.

Table S1 Discontinuations from Single-blind Phase

Number (%) of subjects	Sildenafil 50 mg + Placebo
Related to study drug	
Adverse event	4 (0.8%)
Not related to study drug	
Adverse event	2 (0.4%)
Other	3 (0.6%)
Subject defaulted[a]	7 (1.4%)

[a]Subject was lost to follow up or was no longer willing to participate in study

A total of 475 subjects received treatment in the double-blind phase of the study as summarized in Table S2.

Table S2 Subject Evaluation Groups, Double-blind Phase

Number (%) of subjects)	Sildenafil 50 mg + Placebo n (%)	Sildenafil 100 mg + Placebo n (%)
Treated	239	236
Completed	237 (99.2)	236 (100.0)
Discontinued	2 (0.8)	0 (0)

Two (0.8%) subjects discontinued from the double-blind phase of the study due to AEs (1 was considered to be related to the study drug by the investigator and the other was not).

The number of subjects analyzed for efficacy is summarized in Table S3.

Table S3 Subjects Analyzed for Efficacy

Number (%) of subjects	Sildenafil 50 mg Fixed Dose	Sildenafil 50 mg → 100 mg Titrated Dose	Total
Full Analysis Set, n	240	237	477
Per Protocol, n	84	93	177

All subjects were male (mean age 52.8 years, range 22-80 years) and the majority of subjects were white (479 [97.4%] subjects). A total of 348 (70.7%) subjects had at least 1 disease/syndrome present at the start of the study. The most frequently reported diseases/syndromes (by ≥ 5% of subjects) were hypertension, hyperlipidemia, non-insulin dependent diabetes mellitus, benign prostatic hyperplasia and depression.

Efficacy Results: Subjects who received sildenafil 100 mg + placebo during the double-blind phase of the study had a statistically significantly higher IIEF-EF domain score at the end of treatment compared with subjects who remained on sildenafil 50 mg + placebo throughout the study as summarized in Table S4.

Table S4 Statistical Analysis of Change from Randomisation in IIEF-EF Domain Score, FAS Applying LOCF

	Change from Randomization LS Mean	Comparison of Titrated versus Fixed	
		Difference (95% CI)	p-value
Sildenafil 50 mg → 100 mg Titrated Dose	2.2	1.5 (0.7, 2.4)	<0.001
Sildenafil 50 mg Fixed Dose	0.6		

Analyses of the secondary endpoints were consistent with the results of the primary analysis as summarized in Tables S5**Error! Reference source not found.** and S6.

Table S5 Statistical Analysis of Secondary Endpoints (IIEF Domains, EDITS, QEQ and SEX-Q)

	Comparison of Titrated versus Fixed	
	Difference (95% CI)	**p-value**
IIEF Orgasmic Function Domain Score	0.34 (-0.02, 0.69)	0.062
IIEF Sexual Desire Domain Score	0.4 (0.1, 0.6)	0.002
IIEF Intercourse Satisfaction Domain Score	0.5 (0.1, 0.9)	0.008
IIEF Overall Satisfaction Domain Score	0.5 (0.2, 0.8)	0.002
EDITS Total Score	3.8 (1.4, 6.3)	0.002
QEQ Total Score	3.56 (0.01, 7.11)	0.049
SEX-Q Total Score[a]	3.8 (1.1, 6.6)	0.006

[a]Only the items from the validated SEX-Q questionnaire were used in the analysis.

Table S6 Statistical Analysis of Secondary Endpoints (Event Log Data)

	Odds Ratio (95% CI)	**p-value**
Percentage of occasions at which an erection was hard enough to attempt sexual intercourse	1.24 (0.95, 1.60)	0.1122
Percentage of occasions at which sexual intercourse was attempted	1.29 (1.02, 1.63)	0.0345
Percentage of occasions at which an erection lasted long enough to have successful intercourse	1.29 (1.00, 1.67)	0.0457
Percentage of occasions at which ejaculation and/or orgasm was achieved	1.30 (1.03, 1.64)	0.0247

Safety Results: There were no deaths during the study.

Six subjects experienced on-treatment, serious adverse events (SAEs) during the study as summarized in Table S7.

Table S7 Serious Adverse Events

Subject Number	**Dose**	**Serious Adverse Event**	**Outcome**	**Related to study drug**
Single Blind Phase				
Male, 60 years	Sildenafil 50 mg[a]	Acute vasospastic angiopathy	Recovered	No
Male, 46 years	Sildenafil 50 mg	Urinary infection	Recovered	No
Male, 79 years	Sildenafil 50 mg	Worsening anemia	Recovered	No
Male, 67 years	Sildenafil 50 mg	Carcinoma of the prostate	Not recovered	No
Double Blind Phase				
Male, 53 years	Sildenafil 50 mg	Myocardial infarction	Recovered	No
Male, 57 years	Sildenafil 100 mg[b]	Hypoglycemia	Recovered	No

[a]This subject was not included in the SAEs reported from the clinical study database as he was lost to follow up.
[b]This subject was not included in the SAEs reported from the clinical study database as data from the site was not included in the analyses due to delays in cleaning the data as a result of conflict in the region.

Six subjects discontinued due to AEs as summarized in Table S8.

Table S8 Discontinuations due to Adverse Events

Subject Number	Dose	Adverse Events Leading to Discontinuation	Causality
Single Blind Phase			
Male, 69 years	Sildenafil 50 mg	Ejaculation failure	Study drug
Male, 68 years	Sildenafil 50 mg	Nasal congestion	Study drug
Male, 52 years	Sildenafil 50 mg	Palpitations Visual disturbance Nausea Headache	Study drug Study drug Study drug Study drug
Male, 73 years	Sildenafil 50 mg	Hematoma	Other event – trauma associated with study but not study drug
Double Blind Phase			
Male, 49 years	Sildenafil 50 mg	Headache	Study drug
Male, 53 years	Sildenafil 50 mg	Myocardial infarction[a]	Illness or caused by other illness – coronary angioplasty

[a]Serious adverse event

One subject (male, 46 years) temporarily discontinued the study drug during the single-blind phase of the study due to a urinary tract infection. This was reported as an SAE (Table S7).

The proportion of subjects reporting all causality AEs was similar in each of the treatment groups (between 20 and 23%). The majority (96.6%) of AEs were mild or moderate. The most frequently reported (by ≥ 2% of subjects in any treatment group) AEs are summarized in Table S9.

Table S9 Adverse Events Reported by ≥ 2% Subjects in Any Treatment Group

Percentage of Subjects Reporting All Causality Adverse Events	Sildenafil 50 mg + Placebo. Single-Blind Phase N = 492 n (%)	Sildenafil 50 mg + Placebo. Double-Blind Phase N = 239 n (%)	Sildenafil 100 mg + Placebo. Double-Blind Phase N = 236 n (%)
Headache	32 (6.5%)	17 (7.1%)	7 (3.0%)
Flushing	17 (3.5%)	11 (4.6%)	9 (3.8%)
Hot flush	8 (1.6%)	3 (1.3%)	5 (2.1%)
Dyspepsia	6 (1.2%)	5 (2.1%)	2 (0.8%)

There was a low incidence of AEs related to altered vision. A total of 3 subjects (1 subject receiving sildenafil 50 mg + placebo in the single-blind phase, 1 subject receiving sildenafil 100 mg + placebo in the double-blind phase and 1 subject who reported visual disturbance twice, once during treatment with sildenafil 50 mg + placebo in the single-blind phase and once during treatment with sildenafil 100 mg + placebo in the double-blind phase) reported blurred vision or visual disturbance.

CONCLUSIONS:

Dose titration to sildenafil 100 mg resulted in an improvement in efficacy compared with a fixed dose regimen of sildenafil 50 mg. In addition, all the secondary endpoint results were consistent with the primary endpoint.

Sildenafil, dosed at 50 or 100 mg, was well tolerated. No treatment-related SAEs or deaths were reported during the study. The incidence of AEs was similar in all treatment groups and only 6 (1.2%) subjects discontinued from the study due to AEs. None of these subjects were receiving the 100 mg dose. The most frequently reported AEs (headache and flushing) were consistent with the adverse reactions stated in the Summary of Product Characteristics. Dyspepsia and altered vision were infrequent and not more common at the 100 mg dose than at the 50 mg dose.