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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00159809

PROTOCOL NO.: A1481110

PROTOCOL TITLE: A multi-center, flexible-dose study with a double-blind, randomized, placebo-controlled phase followed by an open-label phase to evaluate the impact of treatment with sildenafil citrate on the symptoms of depression and quality of life (QoL) of male subjects with erectile dysfunction (ED)

Study Center(s): Subjects were enrolled at 31 study centers in Canada.

Study Initiation and Completion Dates: 02 March 2004 to 02 August 2005

Phase of Development: Phase 4

Study Objective(s): *Primary*: Describe the effect of treatment with sildenafil on the depressive symptoms in subjects with ED

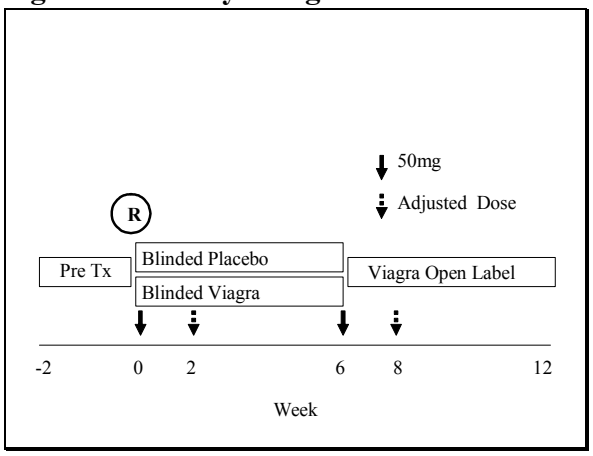
Secondary:

- Measure the improvement in the QoL of subjects with ED treated with sildenafil by the use of an ED-specific instrument
- Describe the effect of treatment with sildenafil on social motivation and behavior of men with ED
- Report the safety of sildenafil
- Describe the relationship between the severity of depression and ED in men of the age of majority consulting for symptoms of ED in the pre-treatment phase
- Describe the effectiveness of sildenafil in the treatment of ED in subjects with dysthymia or NOS depression (excluding mania and MDD)
- Describe the correlation between the Sex Effects (SEX FX) questionnaire and the International Index of Erectile Function (IIEF)
- Validate the Patient Reported Erectile Function Assessment (PREFA) questionnaire (limited validation)

METHODS

Study Design: This was a multicenter, parallel group, flexible-dose study with a 6-week, double-blind, randomized, placebo-controlled phase, followed by a 6-week, open-label phase. A flow chart of the study schedule is presented in Figure S1.

Figure S1. Study Design Flow Chart



R = randomization; Tx = treatment

The study was designed to test the effect of sildenafil on psychological affect in men presenting to their general practitioner's office for symptoms of ED, who were dysthymic or mild to moderately depressed (depression not otherwise specified [NOS]; Beck Depression Inventory II [BDI II] score from 14 to 28 inclusive) at baseline.

The primary outcome was change in BDI II score over the 6-week, placebo-controlled, blinded phase of the study. For secondary outcomes, various metrics were used to analyze mood, sexual interest and sexual function during the blinded and the open-label phases of the study. Safety evaluations were also made in the study.

Number of Subjects (Planned and Analyzed): Assuming that 80% of randomized subjects would contribute to the efficacy evaluable analysis, approximately 70 subjects per treatment group (140 total) were needed to be randomized. (It was anticipated that approximately 700 subjects would be needed for enrollment in the pre-treatment phase in order to select 140 subjects with ED and a BDI II score between 14 and 28.) Of 658 subjects screened, 202 were randomized, including 104 in the sildenafil treatment group and 98 in the placebo group.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were males over the age of majority who had documented ED and who had mild to moderate depression NOS (with a BDI II score from 14 to 28 inclusive). Individuals with major depressive disorder or bipolar depression were excluded, as were those using psychotropic drugs other than benzodiazepines (i.e., antipsychotics, mood stabilizers, antidepressants or lithium), herbal or other remedies for ED, nitrates or nitric oxide donors.

Study Treatment: All subjects were initially prescribed sildenafil citrate (50 mg) tablets or matching placebo during the first 2 weeks of the double-blind treatment phase. Thereafter, the dosage could be adjusted up or down, based on the physician's judgment.

Efficacy Evaluations: The primary efficacy measurement was the change in the Beck Depression Inventory II (BDI II) score from baseline to the end of the blinded phase of the trial. Secondary efficacy measures included the change in BDI II score during the open-label phase, as well as the following psychological and sexual function measures:

- PREFA (Patient Reported Erectile Function Assessment)
- SASS (Social Adaptation Self-Evaluation Scale)
- IIEF (International Index of Erectile Function)
- GEQ (Global Efficacy Assessment Questionnaire)
- Sex Effects (SEX FX)

Safety Evaluations: Adverse events (AEs) were monitored throughout the trial, as were premature discontinuation and concomitant medication use. Hematology, liver function, renal function and electrolytes were assessed at baseline and at the end of the study

Statistical Methods: There were 3 populations for the statistical analysis of data from this study: the Intention to Treat (ITT), the Per Protocol (PP), and the Safety populations. These populations were defined as follows:

1. The ITT population included all subjects who were enrolled in the study, had taken at least 1 dose of study medication and had at least 1 post-baseline measurement. The ITT population was the primary population for the analysis, and was used for the primary and secondary analyses.

2. The PP population was a subset of the ITT population and included subjects who did not have any major protocol deviations as determined by a review of the data after the database was locked. Only the primary analysis was performed on the PP population to confirm results obtained from analyses on the ITT population. Protocol deviations were assessed as follows:

    - Deviations assessed prior to randomization – as per the inclusion criteria, subjects whose BDI II score is outside 14 to 28 at baseline (visit 2) were considered major protocol deviators. This protocol deviation was part of the definition of the PP analysis set.
    - Deviations assessed post randomization – the full list of protocol deviations for the study report was compiled prior to database closure.

3. The safety population included all subjects who received at least 1 dose of study medication.

For the primary endpoint and all other efficacy endpoints except for the Global Efficacy Assessment Questionnaire (GEQ), differences between the 2 treatment groups were analyzed using 2-sided analysis of covariance (ANCOVA). Least Square (LS) means from the ANCOVA model were used to estimate treatment effects, with p-values < 0.05 considered statistically significant.

The model included terms for center, baseline efficacy value, treatment group (sildenafil or placebo), and various predictors: age, smoking status, onset of ED and depression, duration of ED, severity of

ED, duration and severity of depression**.** Two-factor interactions between treatment group and the other model terms were explored.

GEQ data were analyzed using a logistic regression model with covariates as in the primary analysis. Treatment effects were estimated using predicted percents from the model evaluated at the overall mean for continuous covariates (age, duration of ED and depression) and the overall distribution of subjects for categorical covariates (center, smoking status, severity of ED and depression). Efficacy by this measure was analyzed in relation to 1) baseline ED severity, and 2) sildenafil dose at end of study.

RESULTS

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

Table S1. Subject Disposition

Screened Subjects: 658	Double-Blind Phase		Open-Label Phase	
	Sildenafil (N=104) n (%)	Placebo (N=98) n (%)	Sildenafil (N=96) n (%)	Placebo (N=84) n (%)
Assigned to treatment	104 (100.0)	98 (100.0)	96 (100.0)	84 (100.0)
Treated	104 (100.0)	98 (100.0)	96 (100.0)	84 (100.0)
Completed	93 (89.4)	79 (80.6)	93 (96.9)	79 (94.0)
Discontinued	8 (7.7)	14 (14.3)	3 (3.1)	5 (6.0)
Adverse events	0	1 (1.0)	0	0
Other	0	3 (3.1)	0	0
Subject defaulted	8 (7.7)	10 (10.2)	3 (3.1)	5 (6.0)
Analyzed for safety:				
Adverse events	104 (100.0)	98 (100.0)	96 (100.0)	84 (100.0)
Laboratory data	87 (83.7)	73 (74.5)	78 (81.3)	69 (82.1)

None of the 11 cases of discontinuation of treatment in the sildenafil group were considered to be related to the study drug. The only AE leading to discontinuation (in the placebo group during the double-blind phase) was listed as worsening of coronary artery disease.

With the exception of a higher incidence of smokers in the placebo group (32.2% placebo versus 24.5% sildenafil) and a lower incidence of prostate hyperplasia in the sildenafil group (10.2% placebo versus 5.8% sildenafil), subject demographics and baseline characteristics were similar between the sildenafil and placebo groups. Basic demographic characteristics for subjects in the study are summarized in Table S2.

Table S2. Subject Demographic Characteristics

	Double-Blind Phase		Open-Label Phase	
	Sildenafil (N=104)	Placebo (N=98)	Sildenafil (N=96)	Placebo (N=84)
Age (years)				
Mean (SD)	50.8 (10.9)	51.4 (10.9)	50.3 (10.9)	51.5 (10.1)
Range	24 – 76	19 – 76	24 – 76	19 – 76
Race				
Unspecified	104 (100.0)	98 (100.0)	96 (100.0)	84 (100.0)
Weight (kg)				
Mean (SD)	89.7 (16.4)	88.2 (16.2)	89.7 (16.3)	87.1 (14.9)
Range	59.1 – 135.0	53.2 – 138.0	59.1 – 135.0	53.2 – 129.5
Body mass index (BMI)[a]				
Mean (SD)	29.5 (5.4)	29.0 (4.8)	29.3 (5.4)	28.7 (4.4)
Range	21.7 – 48.2	19.9 – 46.1	21.7 – 48.2	21.1 – 39.0
Height (cm)				
Mean (SD)	174.6 (8.3)	174.3 (8.7)	175.1 (8.2)	174.1 (9.1)
Range	147.3 – 198.0	143.0 – 195.6	147.3 – 198.0	143.0 – 195.6

[a] BMI is calculated as weight / (height* .01) **2
SD = standard deviation

Efficacy Results: The results of both primary and secondary efficacy measures are presented in Table S3, below.

Table S3. Primary and Secondary Efficacy Evaluations

	Double-Blind Phase				Open-Label Phase		
	Treatment Arm	Change in LS Mean Scores from BL to 6 Weeks Within Groups (SE)	Difference in LS Mean Scores Between Groups	P-Value	Treatment Arm	Change in Mean Score from 6 to 12 Weeks Within Study Arms (SE)	P-Value
BDI II	Sildenafil	-8.64 (1.22)	4.06	0.0001	sild > sild	-2.87 (0.51)	< 0.0001
	Placebo	-4.57 (1.40)			pbo > sild	-4.86 (0.65)	< 0.0001
PREFA	Sildenafil	6.54 (0.78)	3.69	< 0.0001	sild > sild	1.78 (0.33)	< 0.0001
	Placebo	2.85 (0.9)			pbo > sild	4.44 (0.57)	< 0.0001
IIEF-EF (erectile function domain)	Sildenafil	10.37 (0.92)	7.71	< 0.0001	sild > sild	2.45 (0.59)	< 0.0001
	Placebo	2.66 (1.07)			pbo > sild	9.19 (0.96	< 0.0001
IIEF-EF (orgasmic function domain)	Sildenafil	2.44 (0.32)	1.42	0.0002	sild > sild	0.23 (0.19)	0.2388
	Placebo	1.02 (0.37)			pbo > sild	2.18 (0.35)	< 0.0001
IIEF-EF (sexual desire domain)	Sildenafil	1.50 (0.19)	0.79	0.0007	sild > sild	0.42 (0.15)	0.0051
	Placebo	0.72 (0.22)			pbo > sild	0.97 (0.22)	< 0.0001
IIEF-EF (inter-course satisfaction domain)	Sildenafil	4.95 (0.45)	3.09	< 0.0001	sild > sild	0.98 (0.30)	0.0015
	Placebo	1.86 (0.52)			pbo > sild	3.35 (0.39)	< 0.0001
IIEF-EF (overall satisfaction domain)	Sildenafil	2.88 (0.31)	1.99	< 0.0001	sild > sild	0.70 (0.21)	0.0016
	Placebo	0.88 (0.36)			pbo > sild	2.56 (0.33)	< 0.0001
SASS	Sildenafil	2.41 (0.92)	1.85	0.0197	sild > sild	1.65 (0.48)	0.0008
	Placebo	0.56 (1.07)			pbo > sild	2.30 (0.59)	0.0002
SEX FX – function score	Sildenafil	8.31 (1.21)	3.23	0.0022	sild > sild	2.18 (0.68)	0.0019
	Placebo	5.08 (1.40)			pbo > sild	4.72 (1.01)	< 0.0001
SEX FX – GSI score	Sildenafil	6.05 (0.86)	4.62	< 0.0001	sild > sild	1.86 (0.33)	< 0.0001
	Placebo	1.43 (1.00)			pbo > sild	5.01 (0.70)	< 0.0001

BL = baseline, GEQ = Global Efficacy Assessment Questionnaire, IIEF = International Index of Erectile Function, LS Mean = least square mean, PREFA = Patient Reported Erectile Function Assessment, SASS = Social Adaptation Self-evaluation Scale, SE = standard error, SEX FX = Sex Effects, sild = sildenafil, pbo = placebo

Response to the Global Efficacy Assessment Questionnaire (GEQ): For the first question of the GEQ, 77.3% of subjects in the sildenafil group indicated there was an improvement in their erections after 6 weeks of treatment, while 22.7% of the placebo group indicated there was an improvement in their erections ($p< 0.0001$). For the second question of the GEQ, 75.3% of subjects in the sildenafil group noted improved intercourse after 6 weeks of treatment, while 24.7% of the placebo group indicated there was improvement ($p< 0.0001$). For question 3 of the GEQ, 70% of the subjects in the sildenafil group noted that they obtained an erection that allowed them to engage in satisfactory sexual intercourse "most times" or "always/almost always," as opposed to 30% in the placebo group.

Safety Results: An overview of safety results has been summarized in Table S4, below.

Table S4. Overview of Treatment-emergent Adverse Events (All Causalities)

	Double-Blind Phase		Open-Label Phase		Combined Phases	
	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo
Subjects evaluable for adverse events	104	98	96	84	--	--
Number of adverse events	70	50	33	38	103	88
Subjects with adverse events (%)	43 (41.3)	31 (31.6)	24 (25.0)	27 (32.1)	67	58
Subjects with serious adverse events (%)	2 (1.9)	2 (2.0)	0	0	2	2
Subjects with severe adverse events (%)	4 (3.8)	4 (4.1)	2 (2.1)	1 (1.2)	6	5
Subjects discontinued due to adverse events (%)	0	1 (1.0)	0	0	0	1
Subjects with dose reduced or temporary discontinuation due to adverse events (%)	2 (1.9)	2 (2.0)	1 (1.0)	1 (1.2)	3	3

There were no deaths during the study. Four (4) serious adverse events (SAEs) (2 in each treatment group) occurred during the double-blind treatment period. One SAE in the placebo group (worsening of coronary artery disease) required discontinuation of treatment. The other 3 subjects experienced prostate hyperplasia, cerebral vascular disease and colorectal cancer. None of these SAEs were considered to be study drug-related.

Two subjects in the sildenafil group experienced AEs leading to dose reduction. Both of these subjects experienced mild dyspepsia; 1 of the subjects also experienced 1 event each of mild headache and severe headache. Similarly, 2 subjects in the placebo group experienced severe headache or severe migraine headache. One patient in the placebo group had to stop treatment due to worsening of his coronary artery disease. There were no permanent treatment discontinuations among patients in the sildenafil group.

Table S5, below, summarizes the most frequently occurring (≥ 2 subjects in either treatment group) all-causality AEs during both double-blind and open-label phases of the study.

Table S5. Most Frequently Occurring AEs (≥ 2 Subjects Either Treatment Group) by Phase (All Causalities)

	Double-Blind Phase	
	Sildenafil (N=104) n (%)	**Placebo (N=98) n (%)**
Headache	14 (13.5)	6 (6.1)
Vasodilatation	7 (6.7)	2 (2.0)
Dyspepsia	6 (5.8)	1 (1.0)
Respiratory tract infection	5 (4.8)	1 (1.0)
Rhinitis	4 (3.8)	5 (5.1)
Dizziness	3 (2.9)	1 (1.0)
Albuminuria	2 (1.9)	2 (2.0)
Hot flushes	2 (1.9)	0
Pharyngitis	2 (1.9)	2 (2.0)
Tooth disorder	2 (1.9)	0
Urinary tract infection	2 (1.9)	0
Arthralgia	0	4 (4.1)
Hypertension	0	2 (2.0)
	Open-Label Phase	
	Sildenafil (N=96) n (%)	**Placebo (N=84) n (%)**
Headache	3 (3.1)	8 (9.5)
Flu syndrome	2 (2.1)	1 (1.2)
Respiratory tract infection	2 (2.1)	2 (2.4)
Vasodilatation	1 (1.0)	2 (2.4)
Arthralgia	0	3 (3.6)
Rhinitis	0	3 (3.6)

During the double-blind phase, laboratory tests found evidence of low rates of anemia and liver and kidney dysfunction in sildenafil- and placebo-treated subjects.

CONCLUSIONS:

Over 6 weeks, sildenafil led to significant improvement in the primary endpoint, depressive symptoms as measured by BDI II, compared with the placebo group.

Other efficacy measures of sexual function also improved significantly with sildenafil over this period:

- Psychosocial:
  - Social adaptation (SASS)

- Erectile Function-related:
  - Patient-reported erectile function (PREFA)
  - Erectile function (IIEF-EF)
  - Orgasmic function (IIEF-OF)
  - Sexual desire (IIEF-SD)
  - Intercourse satisfaction (IIEF-IS)
  - Overall satisfaction (IIEF-OS)

- Sexual activities (SEX FX)
- Erections (GEQ and Event-log diaries)

These benefits continued to increase when treatment was extended to a further 6 weeks of open-label sildenafil.

Sildenafil was well-tolerated in this subject population.