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PROPRIETARY DRUG NAME/INN: Viagra®/Sildenafil

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

PROTOCOL NO.: A1481103

PROTOCOL TITLE: A Placebo-Controlled, Randomized, Two-Way Cross-Over, Double-Blind, Flexible Dose, Multicenter Study to Evaluate the Efficacy and Safety of Viagra® in Male Patients with Traumatic Spinal Cord Injury and Erectile Dysfunction

Study Center(s): Six centers in Turkey

Study Initiation and Completion Dates: 16 September 2002 to 5 August 2003

Phase of Development: Phase 4

Study Objective(s): To demonstrate the efficacy, safety and tolerability of Viagra® administered orally, as required, approximately one hour prior to sexual activity to men with erectile dysfunction (ED) associated with spinal cord injury (SCI), as well as its effects on the quality of life (QoL) of these patients.

METHODS

Study Design:

This study was a randomized, double-blind, flexible dose, two-way cross-over study with a washout between cross-over phases. Subjects were males aged 19 years or older with spinal cord injury. Each subject was followed for 16 weeks: a 2-week no treatment run-in period, two 6-week treatment periods, and one 2-week washout period between treatment periods.

After enrollment, each patient entered a no treatment run-in period, during which baseline data on sexual function were collected (baseline, Visit 1, Week -2). Patients then entered the first six-week cross-over period, at the start of which they were randomized to receive a starting dose of either 50 mg sildenafil or corresponding placebo (Visit 2, Week 0). Subjects returned to the clinic after 2 weeks of treatment (Visit 3, Week 2) for consideration of dosage adjustment, and after 6 weeks of treatment (Visit 4, Week 6) for efficacy evaluation. At the end of a two–week washout period, patients then switched treatment groups and commenced the second six-week cross-over period (Visit 5, Week 8). Again, subjects returned to the clinic after 2 weeks of treatment (Visit 6, Week 10) for consideration of dosage adjustment, and after 6 weeks of treatment (Visit 7, Week 14) for efficacy evaluation.

Efficacy measures were assessed at baseline (Week 0), at the end of the first cross-over treatment period (Week 6), at the start of the second cross-over treatment period (Week 8) and at the end of the second cross-over treatment period (Week 14), or at the time of discontinuation of treatment for subjects who discontinued before week 14. Safety and toleration from unsolicited and non-leading questioning were recorded throughout the study.

Number of Patients (planned and analyzed):

A total of 88 subjects were planned for screening in order to have 58 subjects completing the study; Ninety-one subjects were screened, 71 subjects were enrolled and randomized to treatment, and 66 subjects completed the study.

Diagnosis and Main Criteria for Inclusion:

Male subjects, 19 years or older, who had a diagnosis of traumatic SCI at least 6 months prior to screening and who had documented clinical diagnosis of ED (attributable to injury of the spinal cord) confirmed by a Sexual Health Inventory-male (SHI-M) score of 21 or less were eligible for the study. In addition, eligible subjects had to be in a stable relationship for at least the past 6 months and have some psychogenic or reflexogenic erectile function.

Study Treatment:

At the start of the first cross-over period, i.e. Visit 2, male subjects with ED associated with SCI, were randomly assigned to one of the two treatment groups:

- Treatment A: Sildenafil 50 mg tablets
- Treatment B: Corresponding placebo tablets

Study drug was taken on an outpatient basis. Subjects were instructed to take the dose one hour prior to the anticipated sexual activity, but not more than once daily. The starting dose for all subjects was 50 mg. After 2 weeks on treatment, dose escalation to 100 mg was allowed in those patients who tolerated 50 mg but for whom efficacy was insufficient. A dose reduction to 25 mg was only allowed for patients in whom 50 mg was poorly tolerated. At the start of the second cross-over period (Week 8), subjects switched treatment groups, i.e. subjects on Treatment A were given Treatment B, and subjects on Treatment B were given Treatment A. Again, study drug was taken on an outpatient basis, and the same dose adjustment principles were valid as in the first cross-over period. Each cross-over phase was 6 weeks, so maximum exposure to active study treatment was 6 weeks.

Efficacy Evaluations:

Primary endpoint:

- The proportion of subjects who indicated a preference for either treatment (as recorded in the end of study overall efficacy assessment question), and who said that the treatment improved their erections (as recorded in the end of each period efficacy assessment question)

Secondary endpoints:

- Responses to the International Index of Erectile Function (IIEF)
- Responses to the Global Efficacy Assessment (GEA) Question
- Responses to questions on the Quality of Life (QoL) Questionnaire
- Responses to Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) Questions
- Intercourse success rate derived from patient event log.

Safety Evaluations: All observed or volunteered adverse events regardless of suspected causal relationship to study drug were recorded. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) were also recorded as adverse events.

Statistical Methods: The primary efficacy variable (a single proportion of those patients who prefer active to placebo at the end of the study) was analyzed using the binomial test for single proportion with null hypothesis of 50%/50% preference for active medication and placebo. The proportion of subjects who preferred active treatment (or placebo) was calculated by dividing the number of subjects who had a preference for active treatment (or placebo) by the total number of subjects who had a preference for treatment (active or placebo). The subjects who had no preference or had missing preference data were excluded from this analysis. The secondary efficacy endpoints were analyzed using the analysis of variance method appropriate for a two-period, two-treatment cross-over design. This analysis allowed for variation due to sequences, patients, periods, and treatments. All tests of hypotheses were performed at the 5% significance level, and were two-sided. No adjustments were made to nominal significance levels to account for multiple secondary endpoints.

Analyses of the primary measure of efficacy were performed on both the Intent-To-Treat (ITT) and the Evaluable populations. The secondary efficacy measures were analyzed using the ITT population only. The ITT population included subjects who took at least one dose of study medication and had at least one available evaluation during the cross-over treatment period for the variable concerned; the last observation carried forward (LOCF) rule was used for evaluating dropouts. The Evaluable population subset were subjects who completed the study, had efficacy measurements made at appropriate times and under appropriate conditions, and did not violate the study protocol in any fundamental way.

RESULTS

Subject Disposition and Demography:

Subject disposition and demography is shown below in Table S1.

Table S1 Subject Disposition, All Treated Subjects

Number (%) of Subjects	Sildenafil to Placebo	Placebo to Sildenafil
Screened 91		
All Randomized 71		
Treated	35	36
Completed Study	34	32
Discontinued from Study	1	4
Death	1	0
Not willing to participate	0	4

Twenty-five subjects withdrew from the study, 20 during the screening phase and 5 during the double-blind treatment phase. The reasons for withdrawal of the 25 subjects were death (1 subject), not meeting the inclusion criteria (12 subjects), and not willing to participate in the study (12 subjects).

The mean age of the study subjects was 38.1 ± 8.1 years. There was no significant difference between the treatment groups' sociodemographic characteristics (including age, weight, blood pressure, and alcohol and tobacco use), or basal values of vital signs, physical examination values, laboratory measurements, and neurological and erectile response evaluations of study groups. Basal SHI-M score was 10.2 (±5.5) for the group randomized to receive sildenafil first (Sildenafil to Placebo group) and 9.8 (±4.9) for the subjects randomized to receive placebo first (Placebo to Sildenafil group). Erectile dysfunction was essentially organic erectile dysfunction; only one subject (who received sildenafil first) had organic/psychogenic erectile dysfunction.

Efficacy Results: The primary efficacy variable (the proportion of patients who prefer active treatment to placebo) was analyzed using the Binomial test for single proportion. Of 66 evaluable subjects, 28 had a treatment preference. Significantly, all 28 subjects who had a treatment preference selected sildenafil as their treatment preference. Thus, sildenafil was preferred statistically significantly over placebo ($p < 0.001$).

Since the primary efficacy variable (the proportion of patients who prefer active treatment to placebo) was derived from data collected at two time points (at the end of two cross-over periods), first sequence (period) and carryover effects were evaluated using three approaches.

First, the overall proportions (active treatment plus placebo) of "Yes" responses to GEA Question #1 at the end of the first cross-over period and at the end of the second cross-over period were compared (Table S2).

GEA Question #1: "*Compared to having no treatment at all for your erection problem, has the medication you have been taking over the past 4 weeks improved your erections?*"

Table S2 GEA Question #1 Responses: First Period Versus Second Period Cross Tabulation

			GEA Question #1, Second Period		
			Yes	No	Total
GEA Question #1, First Period	Yes	Count	28	15	43
		Row Percent	65.1%	34.9%	100.0%
		Column Percent	68.3%	60.0%	65.2%
	No	Count	13	10	23
		Row Percent	56.5%	43.5%	100.0%
		Column Percent	31.7%	40.0%	34.8%
Total		Count	41	25	66
		Row Percent	62.1%	37.9%	100.0%
		Column Percent	100.0%	100.0%	100.0%

p=0.85, McNemar's Test

The proportion of subjects having improved erections was similar in each period (p=0.85), indicating no period effect.

For the second approach, the proportions of "Yes" responses to GEA Question #1 at the end of the first cross-over period and at the end of the second cross-over (study group sequence) were compared for each treatment (sildenafil and placebo). Results of Study Group versus Treatment are provided separately for sildenafil (Table S3) and placebo (Table S4).

Table S3 Study Group Versus Sildenafil: GEA Question #1 Responses Cross Tabulation

			Sildenafil GEA Question #1 Response		
			Yes	No	Total
Study Group	Sildenafil → Placebo	Count	28	6	34
		Row Percent	82.4%	17.6%	100.0%
		Column Percent	50.0 %	60.0%	51.5%
	Placebo → Sildenafil	Count	28	4	32
		Row Percent	87.5%	12.5%	100.0%
		Column Percent	50.0%	40.0%	48.5%
Total		Count	56	10	66
		Row Percent	84.8%	15.2%	100.0%
		Column Percent	100.0%	100.0%	100.0%

p=0.73, Fisher's exact test

Table S4 Study Group Versus Placebo: GEA Question #1 Responses Cross Tabulation

			Placebo GEA Question #1 Response		
			Yes	No	Total
Study Group	Sildenafil → Placebo	Count	13	21	34
		Row Percent	38.2%	61.8%	100.0%
		Column Percent	46.4%	55.3%	51.5%
	Placebo → Sildenafil	Count	15	17	32
		Row Percent	46.9%	53.1%	100.0%
		Column Percent	53.6%	44.7%	48.5%
Total		Count	28	38	66
		Row Percent	42.4%	57.6%	100.0%
		Column Percent	100.0%	100.0%	100.0%

p=0.48, Chi-square test

No period/carryover effect was found for either cross tabulation analysis, indicating subject responses to sildenafil and placebo were independent of the period in which the treatment was received.

In the third approach, the proportion of subjects who had a preference for any treatment (treatment preference exists) was compared across study group sequences (Sildenafil to Placebo versus Placebo to Sildenafil) and for active treatment (Table S5). This analysis could not be repeated for placebo treatment since there were no subjects who preferred placebo.

Table S5. Study Group Versus Existence of Treatment Preference Cross Tabulation

			Treatment Preference Exists		
			Yes	No	Total
Study Group	Sildenafil -> Placebo	Count	19	15	34
		Row Percent	55.9%	44.1%	100.0%
		Column Percent	50.0%	53.6%	51.5%
	Placebo -> Sildenafil	Count	19	13	32
		Row Percent	59.4%	40.6%	100.0%
		Column Percent	50.0%	46.4%	48.5%
Total		Count	38	28	66
		Row Percent	57.6%	42.4%	100.0%
		Column Percent	100.0%	100.0%	100.0%

p=0.77, Chi-square test

Again, no period effect was found, and subjects who had a preference were equally distributed across study groups. Thus, all three analyses indicate a non-significant (type I error level at 0.05) difference between periods and establish that the primary efficacy analysis is not biased by the presence of carryover and/or period effects.

Safety Results:

Adverse events (all causality) occurring in ≥2% of subjects in either treatment group are shown in Table S6. Most were mild or moderate in severity.

One death (traffic accident) occurred in a subject in the Sildenafil to Placebo group. One serious adverse event (SAE) related to study drug occurred in a subject who had begun sildenafil treatment 10 days before the adverse event; the subject developed massive urethral bleeding when inserting a catheter several hours after intercourse. A voiding cystography revealed some narrowing at a small portion of the neck of the urethra and some "false roots" from improper catheter insertion in the past.

Table S6. Incidence of Adverse Events Occurring in ≥ 2% of Subjects in Either Treatment Group - Safety Population

Body System (Preferred Term)	Sildenafil n = 67		Placebo n = 69	
	n	(%)	n	(%)
Body as a Whole	**19**	**(28.4)**	**8**	**(11.6)**
Abdominal pain	2	(3.0)	1	(1.4)
Accidental injury	4	(6.0)	1	(1.4)
Asthenia	5	(7.5)	2	(2.9)
Flu Syndrome	2	(3.0)	0	
Headache	6	(9.0)	4	(5.8)
Medical/surgical procedure	4	(6.0)	0	
Cardiovascular	**3**	**(4.5)**	**1**	**(1.4)**
Palpitation	2	(3.0)	1	(1.4)
Digestive System	**9**	**(13.4)**	**6**	**(8.7)**
Dyspepsia	4	(6.0)	1	(1.4)
Nausea	2	(3.0)	0	
Nervous System	**6**	**(9.0)**	**3**	**(4.3)**
Dizziness	2	(3.0)	0	
Hypesthesia	2	(3.0)	1	(1.4)
Respiratory	**4**	**(6.0)**	**9**	**(13.0)**
Cough increased	2	(3.0)	3	(4.3)
Respiratory tract infection	2	(3.0)	6	(8.7)
Skin and Appendages	**3**	**(4.5)**	**5**	**(7.2)**
Skin ulcer	3	(4.5)	3	(4.3)
Urogenital	**11**	**(16.4)**	**11**	**(15.9)**
Urinary incontinence	2	(3.0)	2	(2.9)
Urinary tract infection	8	(11.9)	9	(13.0)

CONCLUSION(S)

Of 66 males who had traumatic spinal cord injury and erectile dysfunction and who completed this 16-week double-blind, cross-over study, 28 showed a preference for treatment. All 28 subjects who had a treatment preference (100%) preferred sildenafil to placebo ($p < 0.001$). Additional analyses established no period/carryover effects regarding this conclusion. Only one

serious adverse event related to the study drug was reported (massive urethral bleeding upon self-catheterization); however, this adverse event developed in a subject who had a background of improper self-catheterization practices.

Based on a report completed on: 7 December 2004