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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

NCT NO: 00245596

PROTOCOL NO: A1481210

PROTOCOL TITLE: An Open-Label, Multicentre Study to Measure Treatment Responsiveness of Quality of Sexual Life Questionnaire in the Female Partner of Men With Erectile Dysfunction Treated With Viagra® (Sildenafil Citrate)

Study Centers: The study was conducted at 12 centres in France.

Study Initiation and Completion Dates: 09 March 2006 - 08 January 2007

Phase of Development: Phase 4

Study Objectives: *Primary objective*: To investigate treatment responsiveness of a new quality of sexual life questionnaire for female partners of men with erectile dysfunction. *Secondary objectives*: To investigate the correlation between erectile dysfunction (ED) patient's partner quality of sexual life changes and patient's efficacy measures; to investigate the correlation between ED patient's partner quality of sexual life changes and patient reported outcomes of self-esteem, confidence and relationships.

METHODS

Study Design: This was an open label multicentre, flexible dose, 16-week study. In total 130 subjects (67 couples) were recruited at 12 centres in France. Following the 2-week screening phase, ED subjects received Viagra® on an outpatient basis during a 14 week period. All ED subjects were prescribed 50 mg Viagra® as required during the first 2 weeks of the study. Depending upon safety, efficacy and toleration, the dose could be increased to 100 mg or reduced to 25 mg at Visit 3, if necessary. A total of 6 study visits were scheduled. Following Visit 2 (baseline, Week 0), ED subjects returned to the investigator's office for visits after 2, 6, 10 and 14 weeks of treatment. The partners were present for the screening, baseline and final visits.

ED subjects were assessed using the Self-Esteem / Overall Relationship (SEAR) questionnaire, International Index of Erectile function (IIEF) questionnaire and the Erectile

Dysfunction Inventory for Treatment Satisfaction (EDITS) and global efficacy assessment questions (GEQs). The partners completed the Index of Sexual Life (ISL) questionnaire and the Partner EDITS.

Number of Subjects (Planned and Analysed): The study was designed to include approximately 60 ED subjects (120 male and female subjects in total). A total of 134 male and female subjects were screened and of these, 130 were assigned to treatment. A total of 64 ED subjects took at least one dose of treatment.

Diagnosis and Main Criteria for Inclusion: The study enrolled male subjects aged ≥ 18 years old, clinically diagnosed with ED using the IIEF (score ≤ 25), who had been in a stable relationship with the same female partner for at least 6 months prior to screening. Female partners had to be aged ≥ 18 years old.

Study Treatment: ED subjects were instructed to take one Viagra® tablet (sildenafil citrate) when required approximately one hour before sexual activity, but no more than once daily. All ED subjects were prescribed 50 mg Viagra® as required during the first 2 weeks of the study. Thereafter, depending upon safety, efficacy and toleration, the dose could be increased to 100 mg or reduced to 25 mg at the next visit (Visit 3), if necessary. Other concomitant medications, which could have had an effect on erectile function, remained constant during the study unless changes were medically required. No such drug treatment was to be started during the study

Efficacy Evaluations: ED Subject Assessment: the IIEF and SEAR questionnaires were completed at baseline and end of treatment. The EDITS questionnaire and GEQs were completed at end of treatment and the Subject Event Log was completed every time subjects took medication.

Female Partner Assessment: the ISL questionnaire was completed by the female partners at baseline and Week 14. The Partner EDITS and the female partner treatment continuation question (an independent question derived from the EDITS questionnaire assessing the willingness from ED subject's partner for the ED subject to continue the treatment) were completed at end of treatment only.

Safety Evaluations: For ED subjects, clinical and adverse event (AE) monitoring was performed at all visits. Physical examination including blood pressure and heart rate were performed at screening. For the partners, physical examination was performed at screening. Blood samples for routine laboratory tests were not collected during this study.

Statistical Methods: The primary endpoint was the score of the sexual life satisfaction (SLS) domain of the ISL questionnaire of the ED subject's partner. The primary analysis was based on a paired t-test of the mean change in the SLS domain score between baseline and Week 14, assuming a Normal distribution. A 95%, 2-sided confidence interval (CI) was produced to compare the result with the expected value of 3 points of improvement. For subjects who discontinued prior to Week 14, a last observation carried forward (LOCF) approach was used for the FAS. The secondary endpoints included IIEF domains, SEAR domains, EDITS Index, GEQs 1, 2 and 3, Male Event Log Endpoints, Global Satisfaction

Assessment question (for ED subjects) and ISL, EDITS questionnaire and the female partner treatment continuation question (for the partners). Safety analyses were performed using the safety population, which consisted of all subjects who were known to have received at least one dose of study medication.

RESULTS

Subject Disposition and Demography: Subject disposition is summarised by treatment in the table below.

Table S1 Subject Disposition, Subjects Analysed and Subjects Withdrawn

	Sildenafil Number of Subjects[c]
Screened	67
Assigned to treatment	65
Treated	64
Completed	57 (89.1)
Discontinued	6 (9.4)
Ongoing[a]	1 (1.6)
Analysed for efficacy	
Per protocol population	53 (82.8)
Full analysis set	57 (89.1)
Analysed for safety	
Adverse events	64 (100)
Safety population	64 (100)
Reasons for Withdrawal	
Related to study drug:	3 (4.7)
Adverse event	2 (3.1)
Lack of efficacy	1 (1.6)
Not related to study drug:	3 (4.7)
Adverse event	1 (1.6)
Other[b]	2 (3.1)

[a]Six ED subjects discontinued from the study and 1 subject was on-going at the cut-off date but was not included in the efficacy analysis since the subject withdrew early from the study [b]Other = partner became pregnant, partner left home or unspecified adverse event [c]includes ED subjects only

The majority of subjects were white (94.5%). The mean age of the ED subjects was 51.5 years and of their female partners was 48.0 years.

Efficacy Results: *Primary Endpoint – SLS Domain score of the ISL Questionnaire*. There was a statistically significant increase in the SLS domain score from baseline to Week 14 for both the full analysis set (FAS) and per protocol (PP) populations.

Table S2 Statistical Analysis of Change from Baseline to Week 14 in Female Partner's SLS/ISL Score

SLS/ISL	**Sildenafil** (N = 57) FAS	**Sildenafil** (N = 53) PP
Mean (SD)	8.3 (6.56)	8.7 (6.60)
95% CI	6.57, 10.1	6.88, 10.5
T-Test	9.57	9.59
p-value	<0.0001	<0.0001

In the FAS, 45 female partners (79.0%) were classed as responders, ie they had an increase in the SLS score of 3 or more, and 12 (21.1%) were non-responders. For the PP population, 43 female partners (81.1%) were classed as responders and 10 (18.9%) were non-responders. None of the individual categorical factors in the Type III analysis of prognostic factors affecting whether a subject responded reached statistical significance for the FAS. For the PP population, sexual life satisfaction at baseline and the IIEF score of the ED subject at baseline were both statistically significant when modeled on their own. Only sexual life satisfaction at baseline was significant when the stepwise regression model was used.

Secondary Endpoints: Moderate correlations were seen in the statistical analysis of the comparisons of:

- male erectile function (EF/IIEF) and female partner sexual life satisfaction (SLS/ISL, Spearman coefficient = 0.541 for the whole population and 0.541 (p = 0.0008) for the subset whose female partner did not refer to any disruption in their sexual life - corresponding to answering "No" to question 1 of the ISL)
- male self esteem (SE/SEAR) and female partner sexual life satisfaction (SLS/ISL, Spearman coefficient = 0.451 (p = 0.0065) for the subset whose partner did not refer to any disruption in their sexual life)
- the change in EF/IIEF and the scores for SEAR Question 3 ("I was satisfied with my sexual performance", Spearman correlation coefficient = 0.742) between baseline and Week 14
- the change in EF/IIEF and the scores for SEAR Question 6 ("I felt confident about performing sexually", Spearman correlation coefficient = 0.692) between baseline and Week 14
- in male erectile function (EF/IIEF) and male treatment satisfaction (male EDITS; Spearman coefficient for comparison = 0.466) at Week 14
- male erectile function (EF/IIEF) and female treatment satisfaction (female EDITS; Spearman coefficient for comparison = 0.478) at Week 14
- ED subject and partner EDITS at Week 14. (A strong correlation was seen for this comparison - Spearman coefficient = 0.777.)

Safety Results: There were no deaths during the study.

Two serious adverse events were reported: one ED subject was hospitalised with a neck injury caused by a fall from a bicycle, and the other ED subject was hospitalised with hyperglycaemia due to underlying diabetes. Both SAEs were not related to the study drug according to the investigator (causality is other).

Two ED subjects (1.6%) discontinued due to adverse events. The first was the subject with the neck injury (previously described; injury not related to the study drug according to the investigator; other causality). The other subject discontinued after 10 days of treatment, following moderate upper abdominal pain and headache; these events were considered related to treatment by the investigator. In addition, a third subject withdrew due to an unspecified adverse event considered related to treatment by the investigator.

Adverse events reported by ED subjects were consistent with known side effects of sildenafil: the most frequently reported adverse events were headache, upper abdominal pain and flushing. The majority of adverse events were mild or moderate in severity. There were 3 severe adverse events: headache (treatment-related), tachycardia (treatment-related) and the neck injury (other causality).

Table S3 Summary of Treatment Emergent Adverse Events in Male Subjects

N = 64	Number of Subjects (%) Reporting	
Adverse Event	**All Causality**	**Treatment Related**
Headache	6 (9.4)	6 (9.4)
Abdominal pain upper	3 (4.7)	3 (4.7)
Flushing	2 (3.1)	2 (3.1)
Back pain	2 (3.1)	0
Bronchitis chronic	2 (3.1)	0

Four female partners reported adverse events. These events were gastro-oesophageal reflux disease, chronic bronchitis, pharyngolaryngeal pain and an abortion.

CONCLUSIONS: The SLS domain score of the ISL questionnaire showed a statistically significant increase from baseline to Week 14 for female partners of male subjects with ED who had taken Viagra® as required prior to sexual activity over the 14 week period, for both the FAS and PP populations. For both populations, the mean change in the female partner's SLS score was an increase of over 8 points from baseline. In the FAS and PP populations, 79% and 81% of female partners, respectively, were classed as responders (ie, they had an increase in the SLS score of 3 or more). In the PP population, sexual life satisfaction at baseline and the IIEF score of the ED subject at baseline were important factors in determining whether subjects responded or not.

There was a strong correlation between male and female satisfaction with treatment. There were moderate correlations between improvements in male erectile function and female partner sexual life satisfaction for the whole population. For a subset of female partners who did not refer to disruption in their sexual lives, there was moderate correlation between improvements in male self-esteem and female partner's sexual life satisfaction. There were also moderate correlations between improvements in male erectile function and both male and female treatment satisfaction.

Adverse events reported by male subjects were consistent with known side effects of sildenafil.