An open, multicenter flexible dose escalation study to evaluate the efficacy and safety of sildenafil administered as required to male patients with erectile dysfunction

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ABSTRACT

Objective: To evaluate the efficacy, satisfaction, safety and tolerability of sildenafil taken as prescribed prior to anticipated sexual activity in male outpatients with erectile dysfunction (ED).
Materials and methods: Two hundred and three adult male with ED participated in a 2-week, no treatment, run-in period followed by a 6-week open treatment period. In the present trial, they received 50 mg of Viagra. The primary efficacy variable was the change from baseline in response to item 3 and 4 of the International Index of Erectile Function (IIEF). The secondary efficacy variables were as follows: response to the other questions of the IIEF, the IIEF domain scores, response to the Global Efficacy Assessment Question (GAQ), the Event Logs of Erectile Function and Erectile Dysfunction Inventory of Treatment Satisfaction Questionnaire.
Results: A total of 203 subjects were screened and 175 subjects received the study drug. A total of 168 subjects completed the study. The percent of improved erection based on the (GAQ) was 84.5%. The mean rate of successful intercourse was 0.6. Almost thirty-seven percent of patients were satisfied with the effect of treatment in their erections at week 2. The treatment satisfaction increased to 83.3 % at the end of the study, after 62.6 % of patients increased dose to 100 mg of Viagra. A total of 7 (4%) subject discontinued the study prior to the final visit. The reasons of discontinuation were: adverse events - 1.1%, lost to follow-up - 1.1%, subject no longer willing to participate - 3. Of the 175 subjects who received Viagra, 34 subjects experienced at least one adverse event.
Conclusions: The results of the analyses of the responses to the primary variable were highly statistically significantly in favour of sildenafil, as well as the results of the analyses of all the secondary efficacy variables. These findings support effectiveness of sildenafil. The adverse event profile of sildenafil in this study was consistent with the labeled adverse events for this product.
Key words: erectile dysfunction, sildenafil, safety, efficacy

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INTRODUCTION

Sildenafil citrate (active ingredient of Viagra and Revatio) is a competitive and selective inhibitor of cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 (PDE5), and thus inhibits the degradation of cGMP without affecting cyclic AMP (cAMP) [1]. Cyclic GMP-specific PDE5 is found in the corpus cavernosum, vascular smooth muscle, and platelets [2]. Sildenafil increases intracellular cGMP through activation of guanylate cyclase.

There is growing evidence that relaxation of the corpus cavernosum mediated by non-adrenergic noncholinergic neurons is attributable to nitric oxide (NO) and cGMP [3].

The predominant form of phosphor-diesterase (PDE), the enzyme responsible for the breakdown of cGMP in the human corpus cavernosal tissue is type 5 [4].

Therefore, sildenafil as a selective inhibitor of PDE5, facilitates the NO-driven relaxation of the smooth muscle of the corpus cavernosum and thus enhances the natural, psychological erectile response to sexual stimulation.

Male erectile dysfunction (ED) is a multifactorial disorder with a number of potential causative mechanisms which can show varying degrees of interdependence. This, in turn, gives us a wide range of diseases associated with ED (diabetes mellitus, ischemic cardiac syndrome, hypertension, spinal cord injury, depression and so on). The number of drug or non-drug treatments can potentially lead to ED (transurethral prostate resection (TURP), radical prostatectomy, treatment with SSRI's or antyhypertensives) [5].

Moreover, age is sometimes associated with ED, without the presence of any evident disorder or drug therapy.

In clinical trials sildenafil appeared to be an effective and safe drug for the treatment of ED. Seventy percent to 90% of patients who received sildenafil reported an improvement in their erections, related with the treatment, compared with 10-30 % of patients who received placebo [6].

Regarding the majority of clinical studies and cause of ED, the proportions of patients who reported an improvement with sildenafil are as follows: psychogenic ED (84%), mixed ED (77%), organic ED (68%), elderly (67%), diabetes mellitus (59%), ischemic cardiac syndrome (69%), hypertension (68%), transurethral prostate resection (TURP) (61%), radical prostatectomy (43%), spinal cord injury (83%), and depression (75%) [7].

The aim of this study was to evaluate the efficacy, satisfaction, safety and tolerability of sildenafil taken as prescribed prior to anticipated sexual activity in adult male outpatients with ED.

MATERIALS AND METHODS

The population eligible for the study was male patients aged 18 years older, with documented clinical diagnosis of ED, in a stable relationship and who gave written informed consent. The patients with genital anatomical deformities that would significantly impair erection, who were prescribed and/or taking nitrates, CYP3A4 inhibitors, who used any other medications or therapies to treat their erectile dysfunction, patients with known history of retinitis pigmentosa, with severe hepatic, renal, hematological impairment, patients with hypotension (a resting sitting blood pressure <90/50 mmHg) or hypertension (BP>170/110 mmHg) or malignant hypertension, with significant cardiovascular disease including cardiac failure, myocardial infarction, unstable angina, stroke, symptomatic or clinically significant cardiac arrhythmias within the last 3 months, as well as patients for whom sexual activity were inadvisable could not participated in this study.

A total of 203 subjects were screened and 175 subjects received study drug. The mean age was 42 (range 21-62) years. A total of 168 subjects completed the study. Seven subjects discontinued the study prior to the final visit. This was a multi-disciplinary, multicenter, open, flexible dose escalation study. There was one investigator in each center, urologist or internist and the investigator screened eligible patients to ensure that 20 patients were entered into the active treatment phase of the study, so that each centre had 20 patients on the study drug. The patients were subject to optional consultation within the centre during the 2 week run-in period (prior to the active treatment phase). Following a 2-week no treatment run-in period, during which baseline data on sexual activity were collected, patients entered a 6-week open treatment period. A total of 4 study visits were planned to provide assessments of efficacy, safety, tolerability, and drug accountability, and to provide patients with additional drug supplies. Following the baseline visit when the study drug was dispensed the patients returned to the clinic for follow-up visits after 2 and 6 weeks of treatment. At each visit, an evaluation was performed.

At weeks 0 (end of run-in) and 6 (end of active treatment), the questionnaires were given to the patient. He was asked to complete the questionnaires at the beginning of each visit and to return them to the investigator. Alternative therapies to treat ED were excluded during this study. Other concomitant medications which could have an impact on erectile function should remained constant during the study, unless changes were required for patient safety. Duration of open study treatment was a 6-week period. The

treatment group received 50 mg of sildenafil.

Patient who experience no adverse events with the 50 mg dose of sildenafil but whose ED was not sufficiently improved at this dose may had their dose increased to 100 mg at the week 2 visit. This decision was made by the investigator, after review of patient reported efficacy and safety data. Patient who responded well at a particular dose were not allowed to receive higher doses. Patients who were on the 50 or 100 mg dose were allowed to decrease dose to the next lowest level only if they experienced intolerable or serious adverse effects.

Patients were instructed to take a dose when required for anticipated sexual activity, but no more than once daily. The following efficacy variables were evaluated: primary-responses to questions 3 and 4 of the International Index of Erectile Function (these questions address the patient's ability to achieve successful intercourse). Secondary: responses to the other questions on the International Index of Erectile Function (excluding questions 3 and 4), responses to the Global Efficacy Assessment Question, intercourse success rate derived from Patient Event Log and responses to ED inventory of treatment satisfaction questionnaire. The change from baseline in the individual item scores of IIEF and the EDITS, as well as the IIEF domain scores and the Event Log intercourse success rate were analysed separately using single sample paired *t*-test. The proportion of patients reporting an improvement in the quality of their erections based on the Global Efficacy Assessment and the proportion of patients who had at least one successful intercourse (from Event Log) were summarized in tables and accompanied by 95% confidence interval. The percentage of attempts at sexual intercourse that were successful was derived from the event log.

RESULTS

Of the 175 subjects who received Viagra, a total of 34 (19.4%) subjects experienced at least one adverse event. The most frequent adverse events were: headache 14(8%), rash erythematous 14 subjects (8%) (Table 1).

Table 1. Incidence and severity of treatment-emergent adverse events (all causalities)

Number of subjects evaluable for adverse events	N	(%)	Mild	Moderate	Severe
Autonomic nervous	1	0.6	0	1	0
mouth dry	1	0.6	0	1	0
Cardiovascular	4	2.3	3	1	0
edema peripheral	1	0.6	0	1	0
hypertension	1	0.6	1	0	0
hypotension	1	0.6	1	0	0
tachycardia	1	0.6	1	0	0
Central and peripheral nervous system	17	9.7	9	6	2
headache	14	8.0	9	3	2
neuralgia	1	0.6	0	1	0
paresthesia	2	1.1	0	2	0
Gastrointestinal	7	4.0	5	1	1
duodenitis	1	0.6	0	0	1
dyspepsia	6	3.4	5	1	0
esophagitis	1	0.6	0	0	1
gastritis	1	0.6	0	0	1
General	6	3.4	2	4	0
asthenia	2	1.1	0	2	0
face edema	1	0.6	0	1	0
influenza-like symptoms	4	2.3	2	2	0
Musculoskeletal	1	0.6	0	0	1
hernia	1	0.6	0	0	1
Psychiatric	4	2.3	2	2	0
anxiety	1	0.6	1	0	0
insomnia	3	1.7	1	2	0
sleep disorder	1	0.6	1	0	0
Respiratory	1	0.6	1	0	0
rhinitis	1	0.6	1	0	0
Skin/appendages	15	8.6	15	0	0
pruritus	1	0.6	1	0	0
rash erythematous	14	8.0	14	0	0
Special senses	3	1.7	2	1	0
tinnitus	1	0.6	0	1	0
vision abnormal	2	1.1	2	0	0
Total preferred term events	63	40	40	17	6

A total of 2(1.1%) subjects who received Viagra discontinued because of adverse events including asthenia, 1 subject (0.6%), influenza-like symptoms, 1 subject (0.6%), duodenitis, 1(0.6%); esophagitis, 1(0.6%); gastritis, 1 (0.6%), and hernia,1 (0.6%). There were no deaths. The primary efficacy variable was the change from baseline in the response to Items 3 and 4 of the International Index of Erectile Function (IIEF) (Table 2).

Table 2. Results of responses to domains on the IIEF

Domain	Mean change from baseline	95% confidence interval	p-value
Erectile function	10.2	9.1-11.3	<0.001
Intercourse satisfaction	4.7	4.2-5.2	<0.001
Orgasmic function	2.7	2.2-3.2	<0.001
Overall Satisfaction	3.0	2.6-3.4	<0.001
Sexual desire	1.3	1.0-1.5	<0.001

The results showed a statistically significant change from baseline in favour of the study drug for both Item 3 (change from baseline, 1.8 ± 1.5 SD; p<0.001; 95% CI, 1.6 to 2.0) and Item 4 (change from baseline, 1.9 ± 1.5 SD; p<0.001: 95% CI, 1.6 to 2.1).

The results were similar and the p-values were the same in the ITT population and the effectiveness evaluable population.

The following secondary efficacy variables were evaluated in the ITT population:

1. Items on the IIEF excluding Items 3 and 4. The results are shown in Table 3.
2. Global Efficacy Assessment Question. A total of 84.5% of the subjects reported an improvement in erections (95% CI, 78.2% to 89.6%).
3. Event Logs of Erectile Function. The mean rate of successful intercourse was 0.6 and the number of subject with at least 1 successful intercourse was 85,1% (95% CI, 79,0% to 90.1% for the last 2 on-treatment visit and for the entire treatment period).
4. Erectile Dysfunction Inventory of treatment Satisfaction (EDITS). A total of 83.3% of the subjects said they were satisfied with the treatment (95% CI, 76.8% to 88.6%). 36.8 % of patients were satisfied with the effect of treatment on their erections at week 2. The treatment satisfaction increased to 83.3 % at the end of the study, after 62.6 % of patients increased dose to 100 mg of Viagra.

Table 3. Results of responses to items on the IIEF excluding items 3 and 4

Item Number	Mean change from baseline	95% Confidence interval	p-value
1	1.8	1.5-2.0	<0.001
2	1.9	1.6-2.1	<0.001
5	1.6	1.4-1.8	<0.001
6	2.0	1.7-2.2	<0.001
7	1.5	1.3-1.8	<0.001
8	1.2	1.0-1.4	<0.001
9	1.3	1.0-1.5	<0.001
10	1.4	1.1-1.7	<0.001
11	0.7	0.5-0.9	<0.001
12	0.6	0.4-0.7	<0.001
13	1.6	1.4-1.8	<0.001
14	1.3	1.1-1.6	<0.001
15	1.3	1.1-1.5	<0.001

DISCUSSION

The main treatment-related adverse events reported in the clinical studies are headache, facial flushing, and dyspepsia. Most of the reports indicate that the events are mild to moderate in severity, and that they are transient in nature. The incidence of adverse events listed is low in the studies where patients were taking Viagra as required no more than once per day, and the overall discontinuation rate due to adverse events is low (<3%) [8]. Approximately 3% of patients receiving up to 100 mg of Viagra have reported transient visual disturbances. These usually present as blue or pink tinges to color vision, or increased perception of bright lights. The events are usually transient and are not associated with changes in visual acuity [9]. In the clinical trials to date, no serious adverse events have occurred that were considered to be related to Viagra treatment. Furthermore, there is no evidence of treatment-related laboratory abnormalities [10]. The dosing regimen in this study required all patients to start treatment at 50 mg. Dose escalation to 100 mg was allowed in those patients who tolerate 50 mg but for whom efficacy was insufficient. A dose decrease to 25 mg was only allowed for patients in whom 50 mg was poorly tolerated.

From studies to date, the maximum well tolerated dose has been 100 mg [11]. Data from ongoing open studies indicate that some patients benefit when the dose is increased from 50 mg to 100 mg [12]. Previous studies also indicated that 25 mg was fully effective in only a small number of patients [13]. The incorporation of dose escalation design in this study allowed the flexibility, based on the efficacy and drug tolerance, for each patient to be treated at his optimal dose. The primary efficacy end point was question 3 and question 4 in

the IIEF. There was a significant improvement in both: the ability to achieve an erection (question 3 of the IIEF - change from baseline, 1.8 ± 1.5 SD; p<0.001; 95% CI, 1.6 to 2.0) and the ability to maintain an erection (question 4 of the IIEF - change from baseline, 1.9 ± 1.5 SD; p<0.001; 95% CI, 1.6 to 2.1).

CONCLUSIONS

The results of the analyses of the responses to the primary variable were statistically significantly in favour of sildenafil and the results of the analyses of all secondary efficacy variables support its effectiveness. The adverse event profile of Viagra in this study was consistent with the labeled adverse events for this product.

Conflicts of interest

We declare that we have no conflicts of interest.

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