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PROPRIETARY DRUG NAME/INN: Viagra®/Sildenafil citrate

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

- For the treatment of erectile dysfunction

PROTOCOL NO.: A1481133

PROTOCOL TITLE: An open label, multi center extension study to evaluate the safety, toleration and sustained efficacy of oral sildenafil administered to women who have been diagnosed with female sexual arousal disorder

Study Center(s): Sixty one (61) study centers in the United States.

Study Initiation and Completion Dates: 14 January 2003 to 18 February 2004

Phase of Development: Phase 3

Study Objective(s): To evaluate the safety and toleration of oral sildenafil administered as required to women with FSAD who successfully completed the 12 week double blind studies A1481123 (pre-menopausal women) or A1481082 (post-menopausal women). Sustained efficacy was also evaluated after three and six months of open label therapy.

METHODS

Study Design: This was an open label, non-comparative, 52 week, flexible dose study. All consenting and qualifying subjects received a starting dose of sildenafil 50mg but this could be increased to 100mg or decreased to 25mg based on the subject's efficacy response or toleration, respectively. Subjects attended the clinic at Weeks 0, 4, 14, 26, 39 and 52 and at follow up if required. The follow up visit was only required for subjects who discontinued due to an adverse event or laboratory findings that could be treatment related.

The original planned sample size was dependent on the number of subjects choosing to enter it following completion of one of the two blinded parent trials preceding it (A1481082 and A1481123), which meant that as many as 600 subjects were qualified to enter this study. A total of 265 subjects did enroll in this study before it was terminated early due to a decision by the sponsor to discontinue development of sildenafil for treatment of female sexual arousal disorder (FSAD).

Diagnosis and Main Criteria for Inclusion: Subjects must have completed studies A1481082 or A1481123 without a major protocol violation. Subjects receiving hormone replacement or selective serotonin reuptake inhibitor therapy had to be on stable doses of these drugs throughout

the study. Subjects had to be in a stable sexual relationship. All treatment related adverse events from the previous study were to be resolved prior to starting this study.

Study Treatment: Sildenafil 25mg tablets, sildenafil 50mg tablets, sildenafil 100mg tablets. Subjects received oral sildenafil 50mg when required, taken one hour prior to sexual activity. The dose could be amended to 25mg or 100mg after the first three weeks based on the subject's safety or efficacy response. They were limited to one dose per calendar day. The total duration of the study was to be 52 weeks.

Efficacy Evaluations: The primary purpose of the study was to assess the safety of sildenafil in women with FSAD over a one year period. Sustained efficacy was also evaluated after three and six months of open label therapy.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: No pharmacokinetic or pharmacodynamic evaluations were performed.

Safety Evaluations: Blood pressure and pulse rate and laboratory safety tests were measured at Weeks 0, 4, 14, 26, 39 (no labs), 52 and follow up if required. Physical examination and, if clinically indicated, a gynaecological examination and Papanicolaou smear were performed at Weeks 0, 52 and follow up if required. Adverse events were recorded throughout the study and at follow up if required.

Statistical Methods: Not applicable.

RESULTS

Subject Disposition and Demography:

Table S1. Evaluation Groups (All Subjects Received Sildenafil)

Entered study		265
Completed study		19
Assessed for safety:	Adverse events	265
	Laboratory tests	236
	Vital signs	265

Because of early study termination, of the 265 subjects who received treatment with sildenafil, only 19 subjects completed the study. All reasons for withdrawal from the study are listed in Table S2, below.

Table S2. Reasons for Study Termination

	Withdrawn n (%)			
	Total Withdrawn	**Subject Defaulted**	**Other (including early study termination)**	**Adverse Events**
Sildenafil (N=265)	246 (92.8)	72 (27.2)	164 (61.9)	10 (3.8)
Related to study drug	5 (1.9)	0	0	5 (1.9)
Not related to study drug	241 (90.9)	72 (27.2)	164 (61.9)	5 (1.9)

There were 246 subjects (92.8%) who discontinued from the study. The majority of subjects, 164 (61.9%), discontinued because the sponsor terminated the study. These subjects are included in the "Other" reasons category. An additional 72 (27.2%) subjects defaulted (this includes those lost to follow up).

All subjects were female with a mean age of 40.2 years (range 21-69) and a mean weight of 78.8kg (range 44-161). The majority of subjects (70.2%) were in the 18 to 44 year age band. The majority of subjects were White (78.5%) and the remaining subjects were Black (11.7%), Asian (0.8%), Hispanic (7.5%) and other (1.5%) races.

Efficacy Results: The primary purpose of the study was to assess the safety of sildenafil in women with FSAD over a one year period. Because of early study termination, efficacy data, taken from subject questionnaires, was not assessed.

Safety Results: The number of subjects who reported treatment emergent adverse events and the number of adverse events is shown in Table S3, below.

Table S3. All adverse events by causality

	Sildenafil subjects evaluable=265		
	Number of subjects	**% of subjects**	**Number of events**
All causality	153	57.7	348
Treatment-related	87	32.8	131

Subjects experienced all causality adverse events most frequently in the body systems Body as a Whole (27.9%), Respiratory (17.7%), Cardiovascular (12.8%) and Urogenital (10.6%). Treatment related adverse events were most frequent in the body systems Body as a Whole (18.1%), Cardiovascular (10.9%) and Respiratory (7.5%).

The most frequently occurring adverse events (>5%) are presented in Table S4, below.

Table S4. Incidence of Adverse Events Occurring in >5% of Study Subjects

All patients receiving treatment	265	
	n (%)	
	All causality	Treatment related
Patients with at least one adverse event	153 (57.7)	87 (32.8)
Adverse event:		
Headache	46 (17.4)	43 (16.2)
Vasodilatation	25 (9.4)	25 (9.4)
Respiratory tract infection	15 (5.7)	0
Rhinitis	22 (8.3)	15 (5.7)

The majority of events were mild or moderate. There were 24 all causality severe events reported by 17 subjects and 6 treatment-related severe adverse events reported by 6 subjects. The treatment related events included 4 cases of headache and single cases of chest pain and dyspepsia.

Ten (10) subjects discontinued from the study due to adverse events. Five (5) events were treatment related and 5 were considered not treatment related. Adverse events resulting in discontinuation are presented in Table S5, below:

Table S5. Adverse Events Leading to Discontinuation

Subject Number	Adverse Event	Treatment Related
1018	Headache, vasodilitation	Yes
1032	Abdominal pain	No
1050	Cholelithiasis	No
1063	Endometrial disorder	No
1080	Headache	Yes
1083	Headache	Yes
1108	Headache	Yes
1110	Arthralgia, arthrosis	No
1170	Headache	Yes
1232	Uterine hemorrhage	No

Six (6) subjects reported serious adverse events, which are listed in Table S6, below.

Table S6. Serious Adverse Events

Subject #	Event	Daily Dosage	Day of Onset	Action Taken
1029	Appendicitis	100 mg	101	None
1169	Left chest pain	100 mg	52	None
1050	Gall stone	100 mg	101	Discontinued
1239	Occipital skull fracture, Fall backwards Blow in face	50 mg	33	None
1035	Left breast mass	50 mg	169	None
1122	Ruptured disc	50 mg	14	None

All subjects with serious adverse events recovered, and none of the serious adverse events were considered related to treatment by the investigator or the sponsor.

There were no deaths reported during the study.

There were 33 of 236 (14%) subjects whose laboratory tests were normal at baseline and abnormal at final visit. The most frequent abnormalities were increased absolute neutrophils and eosinophils. Of the 128 subjects who had an abnormal laboratory test at baseline there were six whose tests were more abnormal at final visit. The most frequent abnormality was increased absolute eosinophils. The median changes in laboratory test data from baseline to last observation showed no change or small changes.

Conclusion(s): The study was terminated early due to the decision by the sponsor to discontinue development of sildenafil for the treatment of FSAD. However, oral sildenafil was well tolerated in this population for the duration of the study with 10 subjects discontinuing due to adverse events, five events were considered treatment related. None of the six serious adverse events were considered related to study drug. There was no evidence of a relationship between any laboratory test result and sildenafil.

Based on a report completed on: 17 August 2004.