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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: PF-00446687

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NATIONAL CLINICAL TRIAL NO.: NCT00479570

PROTOCOL NO.: A8361015

PROTOCOL TITLE: Phase 2A Multi-Centre, Double Blind (3rd Party Open), Placebo Controlled 3-Way Cross-Over Study to Investigate the Effect of Single Doses of PF-00446687 on Sexual Arousal and Sexual Desire in Women Suffering from Female Sexual Dysfunction (FSD).

Study Centers: Three centers in Norway, Sweden and Denmark.

Study Initiation and Completion Dates: 08 August 2007 to 25 February 2008

Phase of Development: Phase 2a

Study Objectives:

- To assess the effect of single doses of PF-00446687 on acute sexual arousal and sexual interest as assessed by questionnaires in post-menopausal women suffering from female sexual dysfunction (FSD).
- To assess the effect of single doses of PF-00446687 on medium-term (1 week) sexual arousal and sexual interest as assessed by a diary in post-menopausal women suffering from FSD.
- To assess variability of response and repeatability of study design between 2 similar doses of PF-00446687.
- To assess the pharmacokinetics (PK) of PF-00446687.
- To assess the safety and toleration of PF-00446687.
- If possible, to assess the effect of PF-00446687 on vaginal blood flow (VBF) using the Heat Wash-out (HWO) technique (1 pre-selected site only).

METHODS

Study Design: This was an exploratory double-blind (3rd party open), placebo controlled, 3-way cross-over study in post-menopausal women suffering from FSD. It was estimated that up to 36 subjects would be randomized into the study for 24 to complete. The study duration per subject was estimated to be around 6 to 8 weeks.

Subjects attended the clinic on 5 or 6 occasions for a screening visit; a familiarization visit (which could take place at the screening visit); Study Periods 1 to 3; and a follow-up visit. The screening visit took place within 28 days of administration of study treatment. The familiarization visit, to familiarize subjects with visual sexual stimulation (VSS) and HWO, could have taken place at the screening visit or at a separate visit before dosing with study treatment.

Study Period 1 was preceded by a 1 week diary run-in period. Each of the 3 study periods consisted of 1 dosing day (which took place at the clinic) after which the subject was administered a diary to complete at home over the next 7 days, recording details of their sexual activities. During the 3 study periods, subjects received 2 doses of PF-00446687 (200 mg) as well as 1 placebo dose (1 treatment in each study period). If the first 200 mg dose of PF-00446687 had been poorly tolerated with an unacceptable degree of AEs, a lower second dose could have been administered in subsequent study periods. Following dosing on each occasion, sequences of neutral (documentary) and sexually explicit (VSS) digital versatile disc (DVD)/video material, and self-assessment of sexual desire and arousal questionnaires were administered. PK samples were taken 180 minutes post-dose (prior to commencing the 60 minutes neutral documentary segment) and prior to the subjects leaving the clinic. A brief qualitative interview was conducted by the investigator (at Study Periods 2, 3, and follow-up) to elicit further information from the subject with regards to the previous treatment experience. The intention of the interview was to give the subject the opportunity to report any additional information which had not been captured in the questionnaires or the daily diary.

The wash-out period between dosing days was at least 1 week. A follow-up visit took place 1 to 2 weeks after completion of Study Period 3. This visit consisted of a physical examination, supine blood pressure and pulse rate measurements, and laboratory safety tests (hematology, clinical chemistry, and urinalysis).

At 1 pre-selected site, VBF measurements (by means of HWO) commenced prior to dosing and continued until completion of the final neutral segment.

Number of Subjects (Planned and Analyzed): It was planned that up to 36 subjects would be randomized into the study for 24 to complete. A total of 25 subjects were screened and 24 subjects were assigned to study treatment.

Diagnosis and Main Criteria for Inclusion: Post-menopausal women aged 45 to 65, who had been in a stable heterosexual relationship for at least 6 months prior to study start, with evidence of female sexual arousal disorder as determined by the Abbreviated Female Sexual

Function Questionnaire (ASFQ) and who experienced personal distress due to FSD as assessed by the Measure of Female Sexual Distress.

Study Treatment: PF-00446687 and placebo were provided by the sponsor as bulk powder for preparation of oral dosing solutions at a designated pharmacy by an appropriately qualified person according to an extemporaneous dispensing record. On Day 1 of each study period, investigator site personnel administered the study treatment dissolved in an appropriate aqueous diluent to a total volume of 240 mL.

Efficacy Evaluations: The primary efficacy evaluations were assessment of levels of sexual arousal and desire in both an acute and mid-term setting.

Female sexual desire and arousal were assessed on the dosing days using the Acute Female Sexual Desire and Arousal Scale (AFSDAS) questionnaire, which contains questions on current level of sexual arousal and desire. Responses were assessed on a scale of 0 (not at all) to 4 (a very great deal). The questionnaire was administered pre-dose (not including the film specific questions); 120 minutes post-dose (not including the film specific questions); and after completion of each of the DVD segments (a total of 8 times during each study period).

Longer term assessments were made using a daily paper diary recording details of subjects' sexual arousal and desire, which was completed for 7 days before Study Period 1 and for 7 days after dosing for each of the 3 study periods. There were 7 efficacy questions for the diary; responses were in the form of 5 pre-defined categories.

Pharmacokinetic and Other Evaluations: Blood samples for PK analysis were collected 180 minutes post-dose and prior to leaving the clinic for each study period.

Heat Wash-Out Technique

At 1 pre-selected site, VBF was measured as mL/(100 g tissue x min) changes from baseline for each of the VSS and neutral segments (including the 120 minutes segment immediately postdose). Additional summaries derived from the HWO technique were also explored.

Safety Evaluations: Adverse event (AE) recording, laboratory tests, blood pressure and pulse rate measurements, and physical examinations (as well as a gynecologic examination for those undergoing VBF measurements) were performed at intervals throughout the study. A 12-lead electrocardiogram was performed at screening.

Statistical Methods: The key efficacy endpoints for this study were arousal and desire questions as assessed by the AFSDAS questionnaire for each of the VSS and neutral DVD segments, and arousal and desire as assessed by the subject diary (Days 1 to 7).

No hypothesis testing was performed and no formal decision rules were applied. The effect of PF-00446687 on sexual arousal and desire was estimated by constructing the 2-sided 80% confidence interval (CI) for the difference in least square (LS) means (PF-00446687 minus placebo) using a mixed-effects analysis of variance (ANOVA) with sequence, period, and treatment as fixed effects and subjects-within-sequence as a random effect. First order

carryover was explored. The variability of response was examined, using the same model, by constructing the 2-sided 80% CI for the difference in LS means between PF-00446687 and the second PF-00446687 dose (or lower second dose of PF-00446687).

Arousal and Desire Domains (AFSDAS)

The change from baseline for each question and for each segment was calculated. In addition, the change from baseline for the efficacy endpoints derived from the "Right now" part of the AFSDAS were calculated. The "Film-Specific" part of the AFSDAS was analyzed as absolute values. This gave 7 "change from baseline" values and 6 "absolute values" for the 14 efficacy endpoints derived from the AFSDAS (change from baseline was not calculated for baseline itself). The baseline was the pre-dose assessment in each period. The 13 derived efficacy endpoints were analyzed by fitting 13 separate mixed effect ANOVA models.

The contrasts of interest were:

- PF-00446687 200 mg versus placebo.
- PF-00446687 200 mg versus second PF-00446687 200 mg dose (or lower second dose of PF-00446687).

LS means and differences in LS means between treatments, standard errors of these differences, and the 2-sided 80% CIs for the differences were presented. No p-values were presented.

Arousal and Desire Questions from the Diary

Arousal and desire diary questions were analyzed in the same way as the arousal and desire domains in AFSDAS. Change from baseline was calculated for each question for each day, and for each of the 14 efficacy endpoints derived from the diary. The baseline diary was the diary administered at screening and completed during run-in.

Other Efficacy Evaluations

The change from baseline in VBF, for each segment, was calculated and analyzed similarly. The baseline VBF was calculated as the average VBF from cycles 2, 3, and 4 during the 2 hours post-dose (no video) segment in each period.

Interim Analysis

An interim analysis was to be performed after completion of 50% of the study periods where assessment of size of the effect was to be calculated. Recruitment was to continue during the interim analysis. Based upon data from the interim analysis, the final number of completed subjects was to be determined (no more than 24 subjects in total were to complete the study). However, the interim analysis was not performed because the planned maximum number of subjects (24 subjects) had already been recruited into the study by the completion of 50% of study visits. Instead, data from the non-HWO subjects were analyzed prior to the completion of all study visits for the HWO subjects. This analysis formed part of an internal review of PF-00446687 conducted by the sponsor prior to completion of the study.

Final analysis was conducted after requirements for final release of randomization codes had been met and the official database was released.

Changes In The Conduct of the Study

During the study, the sponsor was made aware of erroneous dose preparations at 1 study center. On review of the available information by the sponsor, it was determined that doses lower than the planned dose had been administered to 6 subjects at 1 study center. These subjects were administered approximately 185 mg PF-00446687 rather than 200 mg PF-00446687 during both PF-00446687 study periods. In addition, these subjects received placebo doses containing 25 µg of the bittering agent Bitrex (denatonium benzoate) instead of the intended dose of 10 µg. This dose was not considered to represent a safety risk to any of the subjects involved in the study as doses of up to 45 µg Bitrex have been used as placebo components in sponsor clinical studies. Subsequently, the sponsor retrained the pharmacy personnel at this center and reviewed the preparation procedures on an ongoing basis at all centers.

RESULTS

Subject Disposition and Demography: Three clinical study centers, 1 in Norway, 1 in Denmark, and 1 in Sweden, enroled subjects into the study. A total of 25 subjects were screened and 24 subjects were assigned to study treatment. Twenty-three subjects completed the study and 1 subject withdrew from the study after the second study period (placebo) because she was no longer willing to participate in the study.

Subject disposition and data sets analyzed are summarized in Table S1.

Table S1. Subject Disposition and Data Sets Analyzed

Number of Subjects		PF-00446687 (200 mg)[a] First Administration	PF-00446687 (200 mg)[a] Second Administration	Placebo
Screened	25			
Assigned to study treatment	24			
Treated		24	23[b]	24
Completed		24	23[b]	23
Discontinued		0	0	1
Analyzed for pharmacokinetics				
Pharmacokinetics analysis set		24	23	0
Analyzed for efficacy				
Per protocol analysis set		24	23	24
Full analysis set		24	23	24
Analyzed for safety				
Adverse events		24	23	24
Laboratory data		21	9	13
Safety analysis set		24	23	24
Vital signs		24	23	24

[a] Six subjects received approximately 185 mg PF-00446687.
[b] Subject 10021003 withdrew from the study after the second study period (placebo) and did not enter the third study period (second administration of PF-00446687).

Demographic characteristics of subjects assigned to each of the 3 sequences of study periods were similar. All 24 subjects were white females with evidence of female sexual arousal disorder, as determined by ASFQ, and were between the ages of 47 and 63 years. Mean (standard deviation) age of subjects was 53.5 (4.0) years (subjects assigned to sequence 1),

57.5 (3.8) years (subjects assigned to sequence 2) and 54.1 (5.3) years (subjects assigned to sequence 3).

Efficacy Results: Mean total and mean changes from baseline in right-now AFSDAS scores were higher during VSS than during neutral phases for all study periods. Mean changes from baseline in film-specific AFSDAS scores were also higher during VSS than during neutral phases for all study periods. In general, mean total and mean changes from baseline in AFSDAS scores during VSS were higher for subjects after each administration of 200 mg PF-00446687 than after the administration of placebo. Comparisons of the adjusted mean changes from baseline in right-now AFSDAS scores between subjects after the administration of 200 mg PF-00446687 and after administration of placebo showed that CIs did not overlap 0 for VSS-1 and VSS-3. However, responses to the questionnaires were variable. In general, adjusted mean changes from baseline in right-now AFSDAS scores during each VSS and neutral phase were higher for subjects after the first administration of 200 mg PF-00446687 than after the second administration of 200 mg PF-00446687. In general, mean changes from baseline in VBF were greater during VSS than during neutral phases. This is consistent with what was observed for the right-now AFSDAS scores during the VSS and neutral phases. As VBF was only performed on a subset of 6 subjects (HWO subjects), the effect of 200 mg PF-00446687 on VBF needs further examination. No clinically meaningful conclusions could be drawn from the daily paper diary.

Pharmacokinetic Results: Mean plasma concentrations of PF-00446687 were similar at 3 and 5 hours after dosing, and were similar for subjects after each administration of 200 mg PF-00446687.

Safety Results: There were no deaths or discontinuations from the study due to AEs. One subject was admitted to hospital with the SAE of stomach pain during the period between screening and study visit 1. There were no SAEs reported after randomization for any subject in this study. Treatment-emergent AEs (TEAEs) and treatment-related TEAEs were reported in all 3 study periods. TEAEs were reported for 18 subjects after the first administration of 200 mg PF-00446687, 5 subjects after the second administration of 200 mg PF-00446687, and 5 subjects after the administration of placebo. Treatment-related TEAEs were reported for 17 subjects after the first administration of 200 mg PF-00446687, 5 subjects after the second administration of 200 mg PF-00446687, and 4 subjects after the administration of placebo. Three subjects reported severe treatment-related TEAEs after the first administration of 200 mg PF-00446687 and 1 subject reported a severe treatment-related TEAE after the administration of placebo. All other TEAEs were mild or moderate in severity. The most frequently reported TEAEs (all causality and treatment-related) were fatigue, diarrhoea, and nausea. The incidence of TEAEs and treatment-related TEAEs was slightly higher for non-HWO subjects than HWO subjects.

The incidence of all causality and treatment-related TEAEs is summarized in Table S2.

Table S2. Incidence of Treatment-Emergent Adverse Events (All Causalities, Treatment-Related) in ≥2 Subjects in any Study Period

System organ class MedDRA preferred term	PF-00446687 (200 mg)[a] First Administration (N = 24) n	PF-00446687 (200 mg)[a] Second Administration (N = 23) n	Placebo (N = 24) n
General disorders and administration site conditions	**10 (10)**	**3 (3)**	**2 (2)**
Fatigue	8 (8)	2 (2)	1 (1)
Feeling hot	1 (1)	0 (0)	1 (1)
Gastrointestinal disorders	**6 (6)**	**1 (1)**	**0 (0)**
Diarrhoea	4 (4)	1 (1)	0 (0)
Nausea	3 (3)	0 (0)	0 (0)
Vascular disorders	**2 (2)**	**1 (1)**	**0 (0)**
Hot flush	1 (1)	1 (1)	0 (0)
Musculoskeletal and connective tissue disorders	**2 (1)**	**2 (1)**	**0 (0)**
Back pain	1 (0)	1 (0)	0 (0)
Limb discomfort	1 (1)	1 (1)	0 (0)
Investigations	**2 (1)**	**0 (0)**	**1 (1)**
Blood pressure increased	1 (1)	0 (0)	1 (1)
Skin and subcutaneous tissue disorders	**3 (2)**	**0 (0)**	**2 (2)**
Erythema	1 (1)	0 (0)	2 (2)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects evaluable for adverse events; n = number of subjects reporting all causality (treatment-related) treatment-emergent adverse events.
[a] Six subjects received approximately 185 mg PF-00446687.

One abnormal laboratory result was reported as an AE of blood glucose decreased for 1 subject after the first administration of 200 mg PF-00446687. This TEAE was of moderate severity and resolved. One subject reported an AE of blood pressure increased. This mild TEAE was considered to be treatment-related and was resolved during the study. None of the other abnormal laboratory findings, vital signs results, ECG, or physical examination findings was considered clinically significant or was reported as an AE.

CONCLUSIONS: This study demonstrated that:

- Single oral doses of 200 mg PF-00446687 improved acute sexual arousal and sexual interest in post-menopausal women suffering from FSD, assessed using questionnaires.
- It was not possible to draw any conclusions on the effect of single oral doses on medium-term (1-week) sexual arousal and sexual interest based on diary card data.
- Responses to the questionnaires and repeatability of the study design were variable between subjects after the 2 doses of 200 mg PF-00446687.
- Plasma concentrations of PF-00446687 were similar between subjects after each administration of 200 mg PF-00446687 at 3 and 5 hours after dosing.
- Single oral doses of 200 mg PF-00446687 were considered safe and well tolerated in post-menopausal women with FSD.

- VBF, which was measured using the HWO technique, responded well to VSS. As VBF was only performed on a subset of subjects, the effect of single oral doses of 200 mg PF-00446687 on VBF needs further examination.