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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NATIONAL CLINICAL TRIALS NO.: NCT00862888

PROTOCOL NO.: A8361011

PROTOCOL TITLE: A 2-Cohort, Multi-Centre, Randomized, Double Blind (3rd Party Open), Placebo Controlled 4-Way Crossover Study to Assess the Efficacy of Single Oral Doses of PF-00446687 on Erectile Function in Men Suffering from Erectile Dysfunction, Using 100 mg Sildenafil as a Positive Control

Study Centres: Three centres: 2 in the United Kingdom and 1 in Norway

Study Initiation and Completion Dates: 23 July 2007 to 26 February 2008

Phase of Development: Phase 2a

Study Objectives:

- To confirm the efficacy of single oral doses of PF-00446687 200 mg in improving penile erectile activity, utilising the penile plethysmography (Rigiscan® Plus) technique, in males suffering from erectile dysfunction.
- To establish efficacy of lower doses of PF-00446687 in improving penile erectile activity and if possible, determine the dose response, in this population.
- To assess subjective assessment of sexual arousal and desire by means of a questionnaire following single doses of PF-00446687.
- To determine the safety and toleration of PF-00446687 in this population.
- To assess pharmacokinetics (PK) after single doses of PF-00446687 and sildenafil in this population.
- To assess agouti-related protein (AgRP) levels in this population.

METHODS

Study Design: This was a 2-cohort study. Up to 16 subjects with male erectile dysfunction (MED) were to complete Cohort 1 and up to 32 subjects were planned to complete Cohort 2. After analysis of Cohort 1 data, it was decided that 24 subjects with MED were to complete Cohort 2.

For Cohorts 1 and 2, subjects attended screening and familiarisation visits (which may have been combined) within 28 days before study drug administration. There were 4 study periods, with a minimum 7-day washout between each period, and a follow-up visit 7 to 10 days after the final dose of study drug. Each study period involved 1 study visit.

Cohort 1: Cohort 1 consisted of a randomised, double-blind, double-dummy, placebo-controlled, 4-way crossover design. At 2 of the 4 study period visits, subjects were to receive a single dose of 200 mg PF-00446687 with a single dose of sildenafil placebo. At the remaining 2 study period visits, subjects received a single dose of 100 mg sildenafil (the positive control) with PF-00446687 placebo at one visit, and a single dose of sildenafil placebo with PF-00446687 placebo at the other visit.

Data from Cohort 1 were analysed during the interval between cohorts to determine if Cohort 2 was to proceed, and to determine the final design details and dose selection for Cohort 2. After analysis of Cohort 1 data, it was decided that Cohort 2 would proceed and the final design details and dose selection for Cohort 2 were decided as documented in the statistical analysis plan for Cohort 2 (14 Jan 2008) and as detailed below. Separate subjects were recruited into Cohort 2.

Cohort 2: Cohort 2 consisted of a randomised, double-blind, double-dummy, placebo-controlled, partially-balanced incomplete block 4-way crossover design, assessing the dose response of PF-00446687. At 2 of the 4 study period visits, subjects received a single dose of PF-00446687 at one of 3 doses (20, 125 and 175 mg PF-00446687) with a single dose of sildenafil placebo. At the remaining 2 study period visits, subjects received a single dose of 100 mg sildenafil (the positive control) with PF-00446687 placebo and a single dose of PF-00446687 placebo with sildenafil placebo. Subjects were randomised to a dosing sequence and received only 2 of the 3 active doses of PF-00446687.

Subjects from Cohorts 1 and 2 who withdrew from the study were to be replaced if the reason for discontinuation was not safety related.

Number of Subjects (Planned and Analyzed):

Cohort 1: Up to 16 subjects with MED were to complete Cohort 1. A total of 15 subjects were screened, assigned to study treatment and completed the study. No subject was discontinued from the study for any reason.

Cohort 2: Up to 32 subjects were planned to complete Cohort 2. After analysis of Cohort 1 data, it was decided that 24 subjects with MED were to complete Cohort 2. A total of 28 subjects were screened and 24 subjects were assigned to study treatment. One subject withdrew from the study after the first treatment period (placebo) because he was no longer willing to participate.

Diagnosis and Main Criteria for Inclusion: This study included male subjects aged between 18 and 65 years, who had moderate to severe erectile dysfunction (6-16 on the erectile function domain of the IIEF) for at least 6 months before study entry, were known

responders to phosphodiesterase type 5 inhibitors and had been in a stable, heterosexual relationship for at least the last 6 months.

Study Treatment: PF-00446687 was manufactured as a powder. PF-00446687 (and placebo) was administered dissolved in an appropriate volume dependent on dose level. At each study period visit, subjects in Cohort 1 drank a solution containing either 200 mg PF-00446687 or PF-00446687 placebo immediately followed by a tablet of either 100 mg sildenafil or sildenafil placebo. The empty container was rinsed with ambient temperature water. The total volume of liquid the subject was required to drink (including rinsings) was not to exceed 240 mL. Subjects took the sildenafil or sildenafil placebo tablet whole with the rinsing solution.

Of the 15 subjects in Cohort 1, 7 subjects inadvertently received approximately 185 mg PF-00446687 instead of 200 mg PF-00446687 in both 200 mg PF-00446687 treatment periods due to a dosing error.

At each study period visit, subjects in Cohort 2 followed a similar procedure for treatment administration to those in Cohort 1.

Efficacy Evaluations: Penile plethysmography using Rigiscan® Plus was recorded continuously from 30 minutes predose to 5 hours postdose at each study period visit during which sequences of visual sexual stimulation (VSS) and neutral (non-VSS) digital versatile disc (DVD) material was shown starting at 2 hours postdose. A questionnaire, used as a measurement of sexual interest and arousal, was completed by subjects prior to commencing the Rigiscan® recording, 2 hours postdose and after completion of each of the VSS/non-VSS DVD segments (a total of 6 times during each study period visit). A diary was completed for 7 days prior to study period visit 1 and for 7 days after each of the 4 study period visits starting on the day of dosing.

Pharmacokinetic Evaluations: Blood samples for PK analysis were collected at 5 hours postdose at each study period visit to determine plasma concentrations of PF-00446687, sildenafil and UK-103,320, the main metabolite of sildenafil.

Pharmacodynamic Evaluations: Blood samples for PD analysis were collected predose and at 5 hours postdose at each study period visit to determine plasma concentrations of AgRP.

Safety Evaluations: Laboratory safety tests (haematology, biochemistry and urinalysis), full physical examination, blood pressure (BP), pulse rate and a 12-lead electrocardiogram (ECG) were performed at screening and at the follow-up visit. BP, pulse rate and a brief physical examination were performed predose and before discharge from the clinic at each study period visit. Adverse events (AEs) were recorded throughout the duration of the study. A urine drug screen was performed at screening and on admission to the clinic at each study period visit. A breath alcohol test was performed on admission to the clinic at each study period visit.

Statistical Methods: Each cohort was analysed separately according to 2 separate statistical analysis plans.

Efficacy Endpoints for Cohorts 1 and 2: The efficacy analyses included the following penile plethysmography endpoints:

- Duration of erections ≥60% rigidity at the base of the penis and area under the rigidity response curve of erectile activity (AUC) at each of following time sequences: during the 2 hours of no DVD material (pre-VSS-1) and during the first VSS (VSS-1) and neutral (Neutral-1) DVD sessions and the second VSS (VSS-2) and neutral (Neutral-2) DVD sessions.
- Total duration of erections ≥60% rigidity at the base of the penis and AUC for the duration of the combined VSS DVD sessions (VSS-1 + VSS-2).
- Total duration of erections ≥60% rigidity at the base of the penis and AUC for the duration of the combined neutral DVD sessions (Neutral-1 + Neutral-2).
- Total duration of erections ≥60% rigidity at the base of the penis and AUC for the duration of the combined VSS DVD sessions plus the combined neutral DVD sessions (VSS-1 + Neutral-1 + VSS-2 + Neutral-2) (Cohort 2 only).
- Total duration of erections ≥60% rigidity at the base of the penis and AUC for the duration of the post dose time sequences.
- Exploring the dose and/or exposure-response relationship of PF-00446687 (Cohort 2 only). This endpoint will be assessed in a separate PK/PD report.

The non-VSS efficacy analyses included the following endpoints:

- Time of onset of first erection of ≥60% rigidity and a minimum of 5 minutes duration.
- Assessment of sexual interest and mental arousal (assessed on a scale from 0-6). The Sexual Interest and Arousal Questionnaire was administered 6 times at each study visit: at predose, pre-VSS-1, post-VSS-1, post-Neutral-1, post-VSS-2, and post-Neutral-2.
- Diary of Sexual Events. Subjects recorded details of their daily sexual events in a daily diary for 7 days starting on the day of dosing (Day 1).

Cohort 1: No statistical hypotheses were formally tested in this study. No p-values were presented. Instead, 2-sided 80% confidence intervals (CIs) were calculated for the contrasts of interest. Contrasts (differences) of interest were PF-00446687 200 mg versus placebo and sildenafil 100 mg versus placebo.

Cohort 2: The hypothesis tested was the slope of the relationship between doses of PF-00446687 and response with the null hypothesis being zero slope. This test was 2-sided and was performed at the 5% level of significance. Before testing for non-zero slope however, the antecedent test was of the curvilinear nature of the relationship, with the null hypothesis being lack of curvature. Of secondary interest were the estimates of the differences between each dose of PF-00446687 and placebo. These differences were to be derived from a satisfactorily fitting model in continuous dose. However, if such a model was

not found, then the differences were available directly from the ANOVA model treating dose level as categorical and forming the appropriate contrast, together with the associated 2-sided 80% CIs.

No other formal comparisons were planned. The above hypotheses were tested in the mixed linear model framework using polynomial dose terms. However, there was scope for further characterisation of the relationship using non-linear model fitting, for example, with the Emax model, if necessary.

The secondary contrasts (differences) of interest were: PF-00446687 175 mg versus placebo, PF-00446687 125 mg versus placebo, PF-00446687 20 mg versus placebo and sildenafil 100 mg versus placebo.

PK and PD Analysis of Cohorts 1 and 2: PK and AgRP samples (if analysed) were to be summarised. For AgRP, a change at 5 hours postdose relative to predose measurement was to be calculated and summarised. Both summaries were to be presented as simple means. For AgRP, the predose, 5 hours and change means were to be presented by treatment.

Safety Analysis of Cohorts 1 and 2: All safety data (AEs, laboratory safety tests, physical examination, BP, pulse rate, ECGs, urine drug screen and breath alcohol test) were summarised.

RESULTS

Subject Disposition and Demography:

Cohort 1:

Table S1. Subject Disposition and Evaluation Groups: Cohort 1

	PF-00446687 (200 mg)[a]		Sildenafil (100 mg)	Placebo[b]
	First Administration	Second Administration		
Number of subjects				
Screened (N = 15)				
Assigned to study treatment (N = 15)				
Treated	15	15	15	15
Completed	15	15	15	15
Discontinued	0	0	0	0
Analysed for efficacy				
Full analysis set	15	15	15	15
Analysed for safety				
Adverse events	15	15	15	15
Laboratory data	0	3	2	3
ECG	15	15	15	15
Vitals	15	15	15	15

ECG = electrocardiogram; N = number of subjects.
[a]Seven subjects received approximately 185 mg PF-00446687.
[b]Placebo = PF-00446687 placebo with sildenafil placebo.

All subjects were white males with moderate to severe erectile dysfunction as determined by the IIEF. Mean (standard deviation [SD]) age was 52.1 (9.8) years and mean (SD) body mass index was 28.0 (4.0) kg/m^2.

Cohort 2:

Table S2. Subject Disposition and Evaluation Groups: Cohort 2

	Dose of PF-00446687			Sildenafil (100 mg)	Placebo[a]
	20 mg	125 mg	175 mg		
Number of subjects					
Screened (N = 28)					
Assigned to study treatment (N = 24)					
Treated	15	15	16	22	24
Completed	15	15	16	22	23
Discontinued	0	0	0	0	1[b]
Analysed for Efficacy					
Full analysis set	15	15	16	22	24
Analysed for safety					
Adverse events	15	15	16	22	24
Laboratory data	2	2	2	5	4
ECG	15	15	16	22	24
Vitals	15	15	16	22	24

ECG = electrocardiogram; N = number of subjects.
[a]Placebo = PF-00446687 placebo with sildenafil placebo.
[b]One subject withdrew from the study after the first treatment period (placebo) because he was no longer willing to participate.

All subjects were white males with moderate to severe erectile dysfunction as determined by the IIEF. Mean (SD) age was 52.4 (6.3) years and mean (SD) body mass index was 27.9 (4.1) kg/m^2.

Efficacy Results:

Cohort 1: Mean Rigiscan® Plus responses were greater for subjects after both administrations of 200 mg PF-00446687 and after dosing with 100 mg sildenafil than after dosing with placebo. Mean Rigiscan® Plus responses were greater for subjects after the first administration of 200 mg PF-00446687 than after the second administration of 200 mg PF-00446687. Mean Rigiscan® responses were similar for subjects after the first administration of 200 mg PF-00446687 and after dosing with 100 mg sildenafil. The sexual interest and arousal questionnaire was a non-validated tool. The questionnaire appeared to be sensitive to the neutral and VSS phases and the mean questionnaire scores appeared to correlate well with the Rigiscan® Plus results. Mean post-VSS sexual interest and mental arousal scores were higher than post-neutral and pre-VSS-1 scores for all treatment periods. Mean post-VSS sexual interest and mental arousal scores were greater for subjects after dosing with either 200 mg PF-00446687 or 100 mg sildenafil than after dosing with placebo. Mean post-VSS scores were similar for subjects after dosing with 200 mg PF-00446687 and after dosing with 100 mg sildenafil. No clinically meaningful conclusions could be drawn from the diary of sexual events data.

The effect of the lower dose of PF-00446687 (185 mg) on the Rigiscan® Plus and questionnaire responses was analysed post-hoc. In summary, the Rigiscan® Plus questionnaire responses of subjects who received 185 mg PF-00446687 during both of the 200 mg PF-00446687 treatment periods were not significantly affected by the dosing error. The post-hoc analyses are held on file by the sponsor.

Cohort 2: A weak dose-response in mean Rigiscan® Plus results was observed with the greatest response seen for subjects after dosing with 175 mg PF-00446687. However, the response was not considered to be clinically meaningful. Variable efficacy was demonstrated in the sexual interest and mental arousal questionnaire and no dose-response in questionnaire results was observed for subjects after dosing with all 3 doses of PF-00446687 (20, 125 and 175 mg). No clinically meaningful conclusions could be drawn from the diary of sexual events data.

Pharmacokinetic Results:

Cohort 1: Mean postdose plasma concentrations of PF-00446687 were similar after both administrations of 200 mg PF-00446687. Mean plasma concentrations of sildenafil and the main metabolite of sildenafil, UK-103,320, 5 hours after dosing with 100 mg sildenafil were similar to those reported in previous studies.

Cohort 2: Mean postdose plasma concentrations of PF-00446687 increased with doses of PF-00446687. Mean plasma concentrations of sildenafil and the main metabolite of sildenafil, UK-103,320, 5 hours after dosing with 100 mg sildenafil were similar to those reported in previous studies.

Pharmacodynamic Results:

Cohort 1: No mean change from baseline in plasma concentrations of AgRP was observed during any treatment period. No notable difference in AgRP plasma concentrations was observed between the 200 mg PF-00446687 and placebo treatment periods.

Cohort 2: Samples for AgRP plasma concentrations were collected from subjects in Cohort 2 but not analysed because no change from baseline and no difference from placebo in plasma concentrations of AgRP were observed in Cohort 1 subjects after dosing with PF-00446687 200 mg, which was a higher dose than those chosen for Cohort 2.

Safety Results:

Cohort 1: One treatment-emergent adverse event (TEAE) (1 subject), 4 TEAEs (3 subjects), 9 TEAEs (6 subjects) and 1 TEAE (1 subject) were reported after the first administration of 200 mg PF-00446687, after the second administration of 200 mg PF-00446687, after dosing with 100 mg sildenfil and after dosing with placebo, respectively. Of these, 2 TEAEs (second administration of 200 mg PF-00446687), 4 TEAEs (100 mg sildenafil) and 1 TEAE (placebo) were considered to be treatment-related. All TEAEs were mild or moderate in severity. The number of subjects who reported treatment-related TEAEs was almost half the number of subjects who reported all causality TEAEs. A higher number of subjects reported TEAEs after the second administration of 200 mg PF-00446687 than after the first

administration or placebo. However, a lower number of subjects reported all causality and treatment-related TEAEs after both administrations of 200 mg PF-00446687 than after dosing with 100 mg sildenafil. The most frequently reported TEAE (all causality and treatment-related) was headache. None of the TEAEs reported after dosing with 200 mg PF-00446687 were reported for more than 1 subject. Treatment-related TEAEs of hypertension and heart rate decreased (1 subject) and headache (1 subject) were reported after the second administration of 200 mg PF-00446687. These TEAEs were mild in severity and resolved during the study.

Cohort 2: Two TEAEs (2 subjects), 2 TEAEs (2 subjects), 3 TEAEs (3 subjects), 11 TEAEs (8 subjects) and 3 TEAEs (3 subjects) were reported after dosing with 20 mg PF-00446687, 125 mg PF-00446687, 175 mg PF-00446687, 100 mg sildenafil and placebo, respectively. Of these, 1 TEAE (175 mg PF-00446687), 6 TEAEs (100 mg sildenafil) and 1 TEAE (placebo) were considered to be treatment-related. All TEAEs were mild or moderate in severity. The number of subjects who reported treatment-related TEAEs was almost half the number of subjects who reported all causality TEAEs. No notable difference in the number of subjects reporting all causality and treatment-related TEAEs was observed after dosing with PF-00446687 (at any of the 3 doses) or placebo. A lower number of subjects reported all causality and treatment-related TEAEs after dosing with PF-00446687 (at any of the 3 doses) than after dosing with 100 mg sildenafil. The most frequently reported TEAE (all causality and treatment-related) was nasal congestion. Only 1 subject reported a treatment-related TEAE after dosing with PF-00446687 (175 mg). The TEAE (headache) was mild in severity and resolved during the study.

CONCLUSIONS:

- This study demonstrated the efficacy of single oral doses of 200 mg PF-00446687, but not the lower doses of PF-00446687, in improving penile erectile activity.
- A second dose of 200 mg PF-00446687 did not induce the same level of response as the first dose of 200 mg PF-00446687; the reason for this is unknown.
- The sexual arousal and desire questionnaire appeared to be sensitive to the neutral and VSS phases and to correlate well with the Rigiscan® Plus results after single oral doses of 200 mg PF-00446687.
- PF-00446687 was well tolerated and safe at all doses.
- Plasma concentrations of PF-00446687, sildenafil and the main metabolite of sildenafil (UK-103,320) were similar to those determined in previous studies.
- No difference from baseline or placebo in plasma concentrations of AgRP was observed after a single oral dose of 200 mg PF-00446687. Therefore, plasma concentrations of AgRP were not measured after the lower doses of PF-00446687 (20 to 175 mg).