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COMPOUND NUMBER: PF-00592379

PROTOCOL NO.: A7771002

PROTOCOL TITLE: A Randomised Double Blind, Placebo Controlled Balanced 4-Way Crossover Study to Assess the Efficacy of Single Oral Doses of PF-00592379 on Erectile Dysfunction, Using 100 mg Sildenafil as a Positive Control

Study Centers: Two (2) centers took part in the study and randomized subjects, 1 each in United Kingdom and Norway.

Study Initiation and Final Completion Dates: 06 February 2006 to 29 June 2006

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To assess the efficacy of single oral doses of PF-00592379 in improving penile erectile activity in subjects with male erectile dysfunction (MED).

Secondary Objectives:

- To determine the safety and toleration of PF-00592379 in subjects with MED.
- To determine the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of PF-00592379.
- To determine the efficacious dose range of PF-00592379.
- To explore the efficacy of PF-00592379 in an outpatient setting.

METHODS

Study Design: This was a randomized, double-blind, controlled, balanced 4-way crossover study in the male subjects diagnosed with erectile dysfunction. There were 2 cohorts of subjects. Subjects in Cohort 1 received placebo and 3 of 4 active treatments (PF-00592379 0.01 mg, 0.2 mg and 3 mg or sildenafil 100 mg). In Cohort 2, subjects received placebo and 3 of 4 active treatments (PF-00592379 10 mg, 60 mg and 100 mg or sildenafil 100 mg). Subjects attended the clinic for 6 visits – a screening visit, 4 study visits and a follow-up

visit. At the screening visit, subjects were familiarized with the equipment and video material to be used in each study period and were given a diary of sexual events to complete daily for 6 days before the first study period. At the study visits, subjects received either placebo or one of the active treatments and were subjected to 3 visual sexual stimulation (VSS) sessions (1 lasting 60 minutes and 2 lasting 30 minutes each) and 2 neutral video sessions (lasting 30 minutes each). Efficacy evaluations detailed below were completed during these sessions. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities for Cohort 1 and Cohort 2

Protocol Activity	Screen	Treatment Periods 1-4								Follow-Up
				VSS 1	Neutral Phase 1	VSS 2	Neutral Phase 2	VSS 3		
		Predose	Dosing	60 Min	30 Min	30 Min	30 Min	30 Min	Post RigiScan	
Informed consent	X									
Medical history	X[a]									
Physical exam	X[b]	X[c]							X[c]	X
Blood pressure and pulse rate	X	X							X	X
Laboratory safety	X	X								X
Prolactin sample		X							X	
Urinalysis	X	X								X
Urine drugs of abuse	X	X								
ECG	X									X
Alcohol breathalyzer		X								
Genotyping sample		X[d]								
Study treatment			X							
Pharmacokinetic sample		X			X[e]				X	
Pharmacodynamic sample		X			X[e]				X	
Visual sexual stimulation				X		X		X		
Mental arousal questionnaire		X		X[e]	X[e]	X[e]			X	
Neutral video					X		X			
Penile plethysmography		X[f]----------X								
Familiarization with RigiScan and VSS	X									

Table 1. Schedule of Activities for Cohort 1 and Cohort 2

Protocol Activity	Screen	Treatment Periods 1-4								Follow-Up
				VSS 1	Neutral Phase 1	VSS 2	Neutral Phase 2	VSS 3		
		Predose	Dosing	60 Min	30 Min	30 Min	30 Min	30 Min	Post RigiScan	
Self-assessment of Grade 3 or 4 erectile activity				X----------X						
Adverse events		X							X	X
Concomitant medication	X	X								X
Diary of sexual events	X[g]								X[g]	
Discharge from unit									X	

ECG = electrocardiogram, VSS = visual sexual stimulation.

a. Included completion of the International Index of Erectile Function.
b. Included a full physical examination and a height and weight measurement.
c. Brief physical examination.
d. Study Period 1 only.
e. It was to have been done at the end of the session.
f. From 15 minutes predose.
g. It was to have been given to complete between screening and Study Period 1 and between each study period.

Number of Subjects (Planned and Analyzed): A total of 32 subjects were planned, analyzed and treated, 16 each from the United Kingdom and from Norway.

Diagnosis and Main Criteria for Inclusion: Males aged in between 18-65 years, who were diagnosed with erectile dysfunction, and who had a previous good response to an oral treatment for erectile dysfunction were included in the study.

Exclusion Criteria: Subjects with high blood pressure or certain heart conditions (eg, angina, heart failure), regardless of whether treated or not and who were on nitrates or alpha-blocker medications were excluded from the study, as well as subjects who were prescribed and/or taking medication which were contraindicated or cautioned with concomitant intake of phosphodiesterase type 5 inhibitors.

Study Treatment: Each subject received orally the study drug, PF-00592379 or the placebo solution and 1 tablet of sildenafil or matching placebo tablet 15 minutes after initiation of RigiScan monitoring. The placebo oral solution was a matching placebo for PF-00592379 and placebo tablet was a matching placebo for sildenafil. All treatments were taken while the subject remained in a semi-recumbent or sitting position with the RigiScan in place. The subject drank the PF-00592379/placebo oral solution followed by swallowing of sildenafil/placebo tablet medication whole, respectively, and did not chew the tablet. The subject drank a suitable quantity of water (140-240 mL) that was used to rinse the oral solution administration vessel. A thin 'film' of mint could be administered immediately before and after dosing to mask the taste of the solution if necessary.

Efficacy Endpoints:

Primary Endpoint: The natural log of the total duration of erections ≥60% rigidity at the base of the penis during VSS.

The secondary efficacy endpoints were:

- The natural log of the total duration of erections ≥60% rigidity at the base of the penis for all RigiScan sessions (VSS and neutral sessions),
- Area under the rigidity response curve of erectile activity for the duration of the VSS,
- Area under the rigidity response curve of erectile activity for the duration of the total RigiScan sessions (VSS and neutral sessions),
- Time of onset of first erection of ≥60% rigidity and a minimum of 5 minutes duration,
- Incidence and duration of Grade 3 and 4 erections as measured by subjective self-assessment of penile rigidity (on a scale of 1–4),
- Assessment of mental arousal (assessed on a scale from 0-6),
- Diary of sexual events.

Safety Evaluations: Adverse events (AEs) were recorded throughout the study. Laboratory safety tests and blood pressure and pulse rate measurements (supine and standing) were performed at screening, predose for each study period and at the follow-up visit. In addition, blood pressure and pulse rate measurements (supine and standing) were also recorded post plethysmography for each study period. A 12-lead electrocardiogram and full physical examination were performed at screening and follow-up. A brief physical examination was performed at admission and discharge from each study period.

Statistical Methods: The analysis population set used in the study were:

- Full Analysis Set (FAS): It was comprised of all randomized subjects. FAS population was considered as the principal population of efficacy and therefore, all primary and secondary endpoints were analyzed using it.

- Safety Analysis Set: This analysis set comprised of subjects who received at least one dose of study drug.

The primary endpoint was the natural log of the total duration of erections ≥60% rigidity at the base of the penis during VSS. The primary endpoint was analyzed using an analysis of variance (ANOVA). Differences between least Squares treatment means (and standard errors of these differences) were calculated. The contrasts of interest were each dose versus placebo and the differences and confidence intervals (CIs) were back transformed (exponentiated) to give geometric means and 2-sided 80% CI's for the ratio of geometric mean on the original scale. The secondary endpoints were analyzed in the same manner. AE data were clinically reviewed, listed and summarized. Vital signs data were summarized (N, mean, median, minimum and maximum) for predose (baseline), postdose and the change from Baseline (to postdose).

RESULTS

Subject Disposition and Demography: In the Cohort 1, 16 subjects were screened, randomized and treated as summarized in Table 2. In the Cohort 2, 17 subjects were screened and 16 subjects were randomized and treated (Table 3). All randomized subjects completed the study and were analyzed for efficacy and safety in both the cohorts. All the subjects in Cohort 1 and Cohort 2 were White males aged between 35-63 years and 36-64 years respectively.

Table 2. Subject Evaluation Groups – Cohort 1

Number of Subjects	PF-00592379 0.01 mg	PF-00592379 0.2 mg	PF-00592379 3 mg	Sildenafil 100 mg	Placebo
Screened			16		
Assigned to study treatment			16		
Treated	12	11	13	12	16
Completed	12	11	13	12	16
Discontinued	0	0	0	0	0
Analyzed for PK:					
PK	12	11	13	12	0
Analyzed for efficacy:					
Efficacy	12	11	13	12	16
Analyzed for safety:					
Adverse events	12	11	13	12	16
Laboratory data	12	11	13	12	16
Vital signs	12	11	13	12	16
ECG	12	11	13	12	16

ECG = electrocardiogram, PK = pharmacokinetic.

Table 3. Subject Evaluation Groups – Cohort 2

Number of Subjects	PF-00592379 10 mg	PF-00592379 60 mg	PF-00592379 100 mg	Sildenafil 100 mg	Placebo
Screened			17		
Assigned to study treatment			16		
Treated	12	12	12	12	16
Completed	12	12	12	12	16
Discontinued	0	0	0	0	0
Analyzed for PK:					
PK	12	12	12	12	0
Analyzed for efficacy:					
Efficacy	12	12	12	12	16
Analyzed for safety:					
Adverse events	12	12	12	12	16
Laboratory data	12	12	12	12	16
Vital Signs	12	12	12	12	16
ECG	12	12	12	12	16

ECG = electrocardiogram, PK = pharmacokinetic.

Efficacy Results:

Duration of Erections ≥60% Rigidity During VSS

For Cohort 1, none of the doses of PF-00592379 resulted in a statistically significant increase in duration of erections ≥60% during VSS compared with placebo. Sildenafil, administered at a dose of 100 mg as a positive control, did result in a statistically significant increase in duration of erections ≥60% rigidity during VSS compared with placebo (Table 4). The duration of erections ≥60% rigidity during VSS and neutral sessions were similar to the durations recorded during VSS alone. Analysis of the secondary endpoints did not result in any statistically or clinically significant improvements following dosing with PF-00592379 compared with placebo.

Table 4. Duration of Erections ≥60% Rigidity During VSS – Cohort 1

	n	Mean Duration (Minutes)[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	4.55	0.58	0.231, 1.474	0.45
PF-00592379 0.2 mg	11	7.89	1.01	0.386, 2.653	0.99
PF-00592379 3 mg	12	10.03	1.29	0.507, 3.265	0.73
Sildenafil 100 mg	12	39.34	5.05	1.983, 12.843	0.03
Placebo	16	7.80			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

For Cohort 2, PF-00592379 was administered at doses up to 100 mg, but did not result in statistically significant increases in duration of erections ≥60% rigidity during VSS compared with placebo. Sildenafil, administered at a dose of 100 mg as a positive control, did result in a statistically significant increase in duration of erections ≥60% rigidity during VSS compared with placebo (Table 5).

Table 5. Duration of Erections ≥60% Rigidity During VSS – Cohort 2

	n	Mean Duration (Minutes)[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	4.90	1.31	0.544, 3.160	0.69
PF-00592379 60 mg	11	4.78	1.28	0.519, 3.156	0.72
PF-00592379 100 mg	11	3.12	0.83	0.338, 2.061	0.80
Sildenafil 100 mg	12	21.34	5.71	2.365, 13.801	0.01
Placebo	15	3.73			

CIs = confidence interval, n =number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

Analysis of the secondary endpoints showed similar results to that observed with the primary endpoint above.

Area Under the Rigidity at Base Response Curve of Erectile Activity During VSS

For Cohort 1, an increase in area under the rigidity response curve was observed following all doses of PF-00592379 compared with placebo. The largest increase in the PF-00592379 treatment groups was seen following treatment with the highest dose (3 mg). A much larger increase was, however, seen following treatment with sildenafil 100 mg and this increase was the only one that was statistically significant (Table 6).

Table 6. Area Under the Rigidity at Base Response Curve During VSS – Cohort 1

	n	Mean Area Under the Curve	Ratio to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	891	2.04	0.59, 7.02	0.46
PF-00592379 0.2 mg	11	741	1.70	0.47, 6.13	0.59
PF-00592379 3 mg	12	1350	3.10	0.90, 10.71	0.24
Sildenafil 100 mg	12	4606	10.57	3.05, 36.67	0.02
Placebo	16	436			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.

There were greater increases in mean area under the curve (AUC) in both the PF-00592379 0.2 mg and 3 mg treatment groups when only data from subjects who received sildenafil during the study was included (sildenafil population) compared to all subjects. Only treatment with sildenafil 100 mg resulted in a statistically significant increase (Table 7).

Table 7. Area Under the Rigidity at Base Response Curve During VSS – Cohort 1 (Sildenafil Population)

	n	Mean Area Under the Curve[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	8	864	1.35	0.43, 4.25	0.73
PF-00592379 0.2 mg	7	1851	2.89	0.86, 9.78	0.26
PF-00592379 3 mg	8	2061	3.22	1.01, 10.32	0.20
Sildenafil 100 mg	12	4681	7.32	2.61, 20.58	0.02
Placebo	12	639			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

For Cohort 2, there was no increase in area under the rigidity response curve following treatment with any dose of PF-00592379 compared with placebo. The mean AUC was smaller in all PF-00592379 treatment groups compared with placebo. There was a statistically significant increase following treatment with sildenafil 100 mg. The results of the statistical analysis are summarized in Table 8. The results were similar for the sildenafil population. The results from Cohort 2 did not extend the apparent dose response observed in Cohort 1.

Table 8. Area Under the Rigidity at Base Response Curve During VSS – Cohort 2

	n	Mean Area Under the Curve[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	269	0.46	0.14, 1.49	0.40
PF-00592379 60 mg	11	375	0.64	0.19, 2.14	0.64
PF-00592379 100 mg	11	298	0.51	0.16, 1.71	0.47
Sildenafil 100 mg	12	3864	6.65	2.06, 21.46	0.04
Placebo	15	581			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

Area Under the Rigidity at Base Response Curve of Erectile Activity During VSS and Neutral Sessions

For Cohort 1, an increase in area under the rigidity response curve was observed following all doses of PF-00592379 compared with placebo. The largest increase in the PF-00592379 treatment groups was seen following treatment with the highest dose (3 mg). A much larger increase was seen, however, following treatment with sildenafil 100 mg and this increase was statistically significant. The results of the statistical analysis are summarized in Table 9.

Table 9. Area Under the Rigidity at Base Response Curve During VSS and Neutral Sessions – Cohort 1

	n	Mean Area Under the Curve[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	929	2.01	0.58, 7.00	0.47
PF-00592379 0.2 mg	11	754	1.63	0.45, 5.97	0.63
PF-00592379 3 mg	12	1387	3.00	0.86, 10.51	0.26
Sildenafil 100 mg	12	4994	10.79	3.07, 37.98	0.02
Placebo	16	463			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

The increase in mean AUC were higher in the PF-00592379 0.2 mg and 3 mg treatment groups when only data from subjects who received sildenafil during the study was included (sildenafil population). The results of the statistical analysis of the sildenafil population are summarized in Table 10.

Table 10. Area Under the Rigidity at Base Response Curve During VSS and Neutral Sessions – Cohort 1 (Sildenafil Population)

	n	Mean Area Under the Curve[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	8	909	1.36	0.43, 4.33	0.73
PF-00592379 0.2 mg	7	1908	2.86	0.84, 9.77	0.27
PF-00592379 3 mg	8	2136	3.20	0.99, 10.36	0.20
Sildenafil 100 mg	12	5069	7.59	2.68, 21.55	0.02
Placebo	12	668			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

For Cohort 2, there was no increase in area under the rigidity response curve following treatment with any dose of PF-00592379 compared with placebo. The AUC was smaller in all PF-00592379 treatment groups compared with placebo. There was a statistically significant increase following treatment with sildenafil 100 mg. The results of the statistical analysis are summarized in Table 11. The results were similar to the sildenafil population.

Table 11. Area Under the Rigidity at Base Response Curve During VSS and Neutral Sessions – Cohort 2

	n	Mean Area Under the Curve[a]	Ratio to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	282	0.45	0.14, 1.42	0.37
PF-00592379 60 mg	11	405	0.64	0.20, 2.10	0.63
PF-00592379 100 mg	11	345	0.55	0.17, 1.79	0.51
Sildenafil 100 mg	12	4378	6.93	2.18, 22.09	0.03
Placebo	15	632			

CIs = confidence interval, n = number of subjects in prespecified criteria, VSS = visual sexual stimulation.
a. Adjusted geometric mean.

Time to Onset of First Erection of ≥60% Rigidity (VSS and Neutral Sessions)

For Cohort 1, none of the doses of PF-00592379 resulted in a notable decrease in time to onset of first erection of ≥60% rigidity. There was a decrease in time to onset of first erection of ≥60% rigidity following treatment with sildenafil 100 mg compared with placebo (difference = -42.2 minutes). The results of the statistical analysis are summarized in Table 12.

Table 12. Time to Onset of First Erection of ≥60% Rigidity - Censored Data

	n	Difference From Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	40.94	1.66, 80.22	0.18
PF-00592379 0.2 mg	11	15.65	-25.18, 56.48	0.62
PF-00592379 3 mg	12	-5.88	-45.35, 33.59	0.85
Sildenafil 100 mg	12	-42.21	-81.80, -2.63	0.17

CI = confidence interval, n = number of subjects in the specified treatment group.

For Cohort 2, the 60 mg dose of PF-00592379 resulted in a notable decrease in time to onset of first erection of ≥60% rigidity (-33.9 minutes difference from placebo). There was also a notable decrease in time to onset of first erection of ≥60% rigidity following treatment with sildenafil 100 mg compared with placebo (difference = -44.6 minutes). The results of the statistical analysis are summarized in Table 13.

Table 13. Time to Onset of First Erection of ≥60% Rigidity - Censored Data

	n	Difference to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	-1.02	-35.13, 33.08	0.97
PF-00592379 60 mg	11	-33.89	-68.88, 1.11	0.21
PF-00592379 100 mg	11	8.07	-26.99, 43.13	0.77
Sildenafil 100 mg	12	-44.62	-78.82, -10.43	0.10

n = number of subjects in the specified treatment group.

Incidence of Grade 3/4 Erections

For Cohort 1, PF-00592379 at doses of 0.01 mg and 3 mg and sildenafil 100 mg resulted in an increase in the incidence of Grade 3/4 erections. The increase was statistically significant

following treatment with PF-00592379 0.01 mg. The results of the statistical analysis are summarized in Table 14.

Table 14. Incidence of Grade 3/4 Erections – Cohort 1

	n	Difference to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	6.60	5.036, 8.167	<0.0001
PF-00592379 0.2 mg	11	-2.36	-4.073, -0.656	0.08
PF-00592379 3 mg	13	1.73	0.198, 3.262	0.148
Sildenafil 100 mg	12	0.46	-1.002, 1.930	0.68

n = number of subjects in the specified treatment group.

For Cohort 2, none of the doses of PF-00592379 resulted in an increase in the incidence of Grade 3/4 erections. Sildenafil 100 mg did result in an increase, which was statistically significant. The results of the statistical analysis are summarized in Table 15.

Table 15. Incidence of Grade 3/4 Erections – Cohort 2

	n	Difference to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	-0.68	-1.421, 0.058	0.24
PF-00592379 60 mg	12	-1.63	-2.398, -0.855	0.01
PF-00592379 100 mg	12	-1.73	-2.509, -0.948	0.005
Sildenafil 100 mg	12	1.60	0.928, 2.270	0.003

CI = confidence interval, n = number of subjects in the specified treatment group.

Mental Arousal

For Cohort 1 and Cohort 2, the assessment of mental arousal was increased following treatment with all doses of PF-00592379 and sildenafil. In Cohort 1, the largest increases were following treatment with PF-00592379 0.2 mg and sildenafil 100 mg. In Cohort 2, the largest increases were following treatment with PF-00592379 10 mg and sildenafil 100 mg. In Cohort 1, the increase was statistically significant following treatment with sildenafil 100 mg (Table 16). However, in Cohort 2, none of the increases following treatment with PF-00592379 was statistically significant (Table 17).

Table 16. Assessment of Mental Arousal – Cohort 1

	n	Mean Score[a]	Difference to Placebo	80% CI	p-Value
PF-00592379 0.01 mg	12	42.58	0.07	-0.67, 0.81	0.91
PF-00592379 0.2 mg	11	101.43	0.93	0.17, 1.70	0.12
PF-00592379 3 mg	13	46.45	0.15	-0.57, 0.88	0.78
Sildenafil 100 mg	12	177.09	1.49	0.75, 2.24	0.01
Placebo	16	39.83			

CI = confidence interval, n = number of subjects in the specified treatment group.
a. Adjusted geometric mean.

Table 17. Assessment of Mental Arousal – Cohort 2

	n	Mean Score[a]	Difference to Placebo	80% CI	p-Value
PF-00592379 10 mg	12	84.16	0.71	-0.05, 1.47	0.23
PF-00592379 60 mg	12	50.20	0.19	-0.57, 0.95	0.75
PF-00592379 100 mg	12	47.02	0.13	-0.64, 0.89	0.83
Sildenafil 100 mg	12	91.59	0.79	0.03, 1.55	0.18
Placebo	16	41.47			

CI = confidence interval, n = number of subjects in the specified treatment group.
a. Adjusted geometric mean.

For Cohort 1, the mean scores for mental arousal during the VSS and neutral sessions were lower than during the VSS sessions alone. However, the differences to placebo were similar and sildenafil was the only treatment that resulted in a statistically significant increase in mental arousal compared with placebo. Whereas, in Cohort 2, during VSS and neutral sessions, the difference to placebo was smaller for all treatment groups than during the VSS sessions alone. None of the treatments resulted in a statistically significant increase.

Sexual Events

For both the cohorts, there were no significant differences in responses to the questions in the diary of sexual events in the 7 days following dosing for any treatment group. The responses are summarized in Table 18 and Table 19 respectively. The responses to the diary questions were generally higher (with the exception of frequency of sexual activity) during the first 3 days of each diary period.

Table 18. Diary of Sexual Events – Cohort 1

	Screen	PF-00592379 0.01 mg	PF-00592379 0.2 mg	PF-00592379 3 mg	Sildenafil 100 mg	Placebo
Thought about/interested in sex	3.8	3.9	4.4	3.9	3.9	4.5
Did you get an erection today?	1.3	1.0	1.6	1.5	1.6	1.5
Frequency in sexual activity	1.9	1.9	2.4	2.1	2.0	2.4
Percentage of sexual activity leading to intercourse	37.0	43.5	53.8	44.4	54.5	48.7
Percentage of intercourse when erections lasted long enough to complete	40.0	30.0	50.0	66.7	83.3	63.2

In Cohort 2, the percentage of intercourse when erections lasted long enough to complete did increase in all groups including placebo.

Table 19. Diary of Sexual Events – Cohort 2

	Screen	PF-00592379 10 mg	PF-00592379 60 mg	PF-00592379 100 mg	Sildenafil 100 mg	Placebo
Thought about/interested in sex	4.9	5.2	4.8	3.9	5.3	4.9
Did you get an erection today?	2.1	1.8	1.8	1.3	2.0	1.7
Frequency in sexual activity	2.3	1.8	1.8	1.8	2.1	2.6
Percentage of sexual activity leading to intercourse	52.8	54.5	68.2	36.4	48.0	47.6
Percentage of intercourse when erections lasted long enough to complete	47.4	83.3	80.0	100.0	83.3	80.0

Due to lack of efficacy seen at any dose level, it was decided not to analyze the samples for PD markers.

Safety Results:

Approximately 50% of subjects reported 1 or more treatment emergent AEs during the study. The majority of AEs were mild and reported following treatment with sildenafil 100 mg. Of the 16 subjects treated in Cohort 1, 11 reported a total of 25 all-causality AEs during the study. The majority of AEs were reported by a maximum of 1 subject per treatment group. The only AEs reported by >1 subject per treatment group were headache and nasal congestion (each reported by 3 subjects following treatment with sildenafil 100 mg). A summary of all-causality treatment emergent AEs and treatment-related treatment-emergent AEs for Cohort 1 are provided in Table 20 and Table 21, respectively.

Table 20. Treatment-Emergent Adverse Events (All Causality) - Cohort 1

System Organ Class Preferred Term	PF-00592379 (n)			Sildenafil 100 mg (n)	Placebo (n)
	0.01 mg	0.2 mg	3 mg		
	N=12	N=11	N=13	N=12	N=16
Ear and labyrinth disorders	0	1	0	0	0
Vertigo	0	1	0	0	0
Gastrointestinal disorders	0	1	0	1	1
Diarrhoea	0	0	0	0	1
Dyspepsia	0	0	0	1	0
Nausea	0	1	0	1	0
General disorders and administration site conditions	0	1	0	0	0
Fatigue	0	1	0	0	0
Infections and infestations	0	0	0	1	1
Influenza	0	0	0	1	1
Musculoskeletal and connective tissue disorders	0	1	0	0	1
Back pain	0	1	0	0	1
Nervous system disorders	0	1	0	4	2
Dizziness	0	0	0	1	0
Head discomfort	0	0	0	0	1
Headache	0	1	0	3	1
Psychiatric disorders	0	0	0	1	0
Anxiety	0	0	0	1	0
Respiratory, thoracic and mediastinal disorders	1	0	0	5	1
Dyspnoea	0	0	0	1	0
Nasal congestion	0	0	0	3	1
Rhinorrhoea	1	0	0	1	0
Total preferred term events	1	5	0	13	6

Subjects were counted only once per treatment in each row. Includes data up to 30 days after last dose of study drug. MedDRA (v9.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects with adverse events, N = number of subjects evaluable for the adverse event, v = version.

Table 21. Treatment-Emergent Adverse Events (Treatment Related) - Cohort 1

System Organ Class Preferred Term	PF-00592379 (n)			Sildenafil 100 mg (n)	Placebo (n)
	0.01 mg	0.2 mg	3 mg		
	N=12	N=11	N=13	N=12	N=16
Ear and labyrinth disorders	0	1	0	0	0
Vertigo	0	1	0	0	0
Gastrointestinal disorders	0	1	0	1	0
Dyspepsia	0	0	0	1	0
Nausea	0	1	0	1	0
General disorders and administration site conditions	0	1	0	0	0
Fatigue	0	1	0	0	0
Nervous system disorders	0	0	0	3	1
Dizziness	0	0	0	1	0
Head discomfort	0	0	0	0	1
Headache	0	0	0	2	0
Psychiatric disorders	0	0	0	1	0
Anxiety	0	0	0	1	0
Respiratory, thoracic and mediastinal disorders	0	0	0	4	1
Dyspnoea	0	0	0	1	0
Nasal congestion	0	0	0	3	1
Total preferred term events	0	3	0	10	2

Subjects were counted only once per treatment in each row. Includes data up to 30 days after last dose of study drug. MedDRA (v9.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects evaluable for adverse event, n = number of subjects with adverse event, v = version.

In Cohort 2, no AEs were reported by >1 subject per treatment group. The incidences of diarrhea, salivary duct obstruction and fatigue were each reported by one subject in more than one treatment periods. One (1) AE was considered treatment related by the Investigator – stomach ache (upper abdominal pain) reported by 1 subject following treatment with placebo. A summary of all-causality treatment emergent AEs and treatment-related treatment-emergent AEs for Cohort 2 are provided in Table 22.

Table 22. Treatment-Emergent Adverse Events (All Causality) - Cohort 2

System Organ Class Preferred Term	PF-00592379 (n)			Sildenafil 100 mg	Placebo
	10 mg	60 mg	100 mg	N=12	N=16
	N=12	N=12	N=12	(n)	(n)
Gastrointestinal disorders	0	1	1	2	1
Abdominal pain upper	0	0	0	0	1
Diarrhoea	0	1	0	1	0
Salivary duct obstruction	0	0	1	1	0
General disorders and administration site conditions	1	0	1	0	1
Fatigue	1	0	1	0	1
Nervous system disorders	0	0	0	0	1
Syncope	0	0	0	0	1
Total preferred term events	1	1	2	2	3

Subjects were counted only once per treatment in each row. Includes data up to 30 days after last dose of study drug. MedDRA (v9.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities, N = number of subjects evaluable for adverse events, n = number of subjects with adverse event, v = version.

There were no serious AEs, deaths and withdrawals due to AEs reported in this study.

The incidence of laboratory abnormalities was low and no laboratory test abnormality was reported by >1 subject per treatment group. There was no evidence that PF-00592379 resulted in a dose dependent change in vital signs.

CONCLUSION:

PF-00592379 at doses from 0.01 to 100 mg, did not result in a statistically or clinically significant improvement in erectile activity as measured by duration of erections ≥60% rigidity, area under the rigidity at base response curve of erectile activity, time to onset of first erections of ≥60% rigidity, incidence of Grade 3/4 erections (with the exception of PF-00592379 0.01 mg), mental arousal or diary of sexual events. Sildenafil, administered at a dose of 100 mg as a positive control, did result in statistically and clinically significant improvements in erectile activity.

PF-00592379 was well tolerated at all doses tested. There were no discontinuations due to AEs and no severe or serious AEs were reported.