



CLINICAL PROTOCOL

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.

Compound:	PF-00446687
Compound Name:	N/A
US IND Number:	N/A
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PROTOCOL SUMMARY

Indication:

Male erectile dysfunction (MED).

Rationale:

MED is a very prevalent condition and has a significant impact on quality of life, with subjects commonly reporting increased anxiety, loss of self-esteem, lack of self-confidence, tension and difficulty in relationships with their partner.

PF-00446687 is a potent and selective prototype melanocortin MC4 receptor agonist, in development for the p.r.n treatment of female sexual dysfunction (FSD) and MED. There is no precedent for a selective agonist of the MC4 receptor sub-type to treat MED or FSD, however there is clinical precedent for treating both MED (Phase 2b) and FSD (Phase 2a) with non-selective MC receptor agonists. Efficacy in these studies has been limited by poor toleration (significant nausea and vomiting). Pre-clinical data support the hypothesis that selective MC4 agonism could improve the therapeutic window.

A clinical study assessing the pharmacodynamic effect of a single dose of PF-00446687 (3 to 200 mg) on penile erections in 48 healthy male volunteers with no evidence of erectile dysfunction has just been completed. Erectile activity was monitored using the penile plethysmography Rigiscan[®] Plus methodology whilst watching sequences of erotic and non-erotic DVD material. PF-00446687 was well tolerated in this study. Compared with placebo, a modest effect of PF-00446687 200 mg on erectile activity was observed during the visual sexual stimulation and this was of similar magnitude to that of a PDE5i control. Furthermore, a substantial effect on erectile function was observed in the periods without erotic stimulation, supporting a central mechanism of action for this molecule.

Sildenafil is a potent, selective competitive inhibitor of cGMP specific, type 5 PDE, the predominant PDE of the human corpus cavernosum is included in this study as a positive control. Sildenafil enhances relaxation of the penile corpus cavernosum induced by nitric oxide-mediated non-adrenergic non-cholinergic and cholinergic neurotransmission and improves penile erection in MED patients.

Penile plethysmography Rigiscan[®] Plus methodology is an established technique for determining the efficacy of pro-erectile therapies in patients with MED. This technique has been used to determine the effect of phosphodiesterase Type 5 inhibitors, apomorphine, and experimental agents such as the melanocortin receptor agonists Melanotan II and PT-141.

This study will investigate the efficacy of PF-00446687 in MED.

Objectives:

- To confirm the efficacy of single oral doses of PF-00446687 200 mg in improving penile erectile activity, utilizing 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 questionnaire following single doses of PF-00446687.
- To determine the safety and toleration of PF-00446687 in this population.
- To assess PK after single doses of PF-00446687 and sildenafil in this population.
- To assess Agouti Related Protein (AgRP) levels in this population.

Trial Design:

This is a two-cohort study. Up to 16 subjects will complete Cohort 1 and up to 32 subjects will complete Cohort 2.

Cohort 1 will consist of a randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover design. During two of the four study visits, subjects will receive a single dose of PF-00446687 200 mg. During the remaining study visits, subjects will receive sildenafil 100 mg (the positive control) and placebo. Subjects will attend for screening and familiarization visits (which may be combined) and 4 study visits, with a minimum of 7 days washout between study periods. They will be given a paper Diary of Sexual Events to complete in the 7 days leading up to each study visit 1 and for 7 days following each study visit.

Data from Cohort 1 will be analyzed during the interval between cohorts to determine the final design details and dose selection for Cohort 2.

Cohort 2 will consist of a randomized, double-blind, placebo-controlled, 4-way crossover design, assessing dose response of PF-00446687. Sildenafil may or may not be used as a positive control in Cohort 2 (dependent on the outcome of the interim analysis from Cohort 1). Actual doses of PF-00446687 will be determined after the interim analysis but will not exceed 200 mg. Doses may be repeated. The final design (may be complete or incomplete block design) will be determined after analysis of Cohort 1. Should sildenafil be used in Cohort 2, the study will become double-dummy.

Endpoints:

Total duration of erections $\geq 60\%$ rigidity at the base of the penis and area under the rigidity response curve of erectile activity (AUC) for the duration of the post dose time sequences.

Total duration of erections $\geq 60\%$ rigidity at the base of the penis and AUC for the duration of (VSS-1 + VSS-2).

Total duration of erections $\geq 60\%$ rigidity at the base of the penis and AUC for the duration of (Neutral-1 + Neutral-2).

Duration of erections $\geq 60\%$ rigidity at the base of the penis and AUC at each of following time sequences:

- Pre-VSS-1
- VSS-1
- Neutral-1
- VSS-2
- Neutral-2

(Both tip and base data will be databased. In the event of base data being unsuitable for databasing, base data will be imputed from tip data).

Time of onset of first erection of $\geq 60\%$ rigidity and a minimum of 5 minutes duration.

Exploring the dose and/or exposure - response relationship of PF-00446687.

Assessment of sexual interest and mental arousal (assessed on a scale from 0-6).

Diary of Sexual Events.

Trial Treatments:

The treatments to be administered in Cohort 1 are:

- PF-00446687 200 mg with sildenafil placebo
- Repeat PF-00446687 200 mg with sildenafil placebo
- Sildenafil 100 mg with PF-00446687 placebo
- PF-00446687 placebo with sildenafil placebo

The treatments to be administered in Cohort 2 will be determined upon analysis of data from Cohort 1. This may or may not include sildenafil 100 mg. The doses administered of PF-00446687 in Cohort 2 will not exceed 200 mg. No more than 4 study visits will take place in Cohort 2. One of the study visits will be placebo.

Statistical Methods:

Allocation to Treatment

Cohort 1 will be a Williams design with 4 treatments (A, B, C, D) where treatment D has been replaced with a repeat of treatment C.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	C	B	C
Sequence 2	B	A	C	C
Sequence 3	C	B	C	A
Sequence 4	C	C	A	B

Treatment C represents PF-00446687 200 mg and A and B are placebo and sildenafil 100 mg in some order.

Data analysis/statistical methods

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in an Analysis Plan, which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. On review of the data, some of the assumptions underlying the described analysis may not be adequately met so additional exploratory analyses may be performed to more fully understand the data.

Sample Size Determination

Simulations have shown that repeating PF-00446687 200 mg within each subject is expected to increase power from 67% to 83% for the 16 subjects in Cohort 1.

The sample size for Cohort 2 is not expected to exceed 32 subjects, and will be determined (and justified) following review of Cohort 1 data.

Efficacy Analysis

Each cohort will be analysed separately.

For Cohort 1, the VSS endpoints will be analysed on the natural log scale (ln) using a mixed effects analysis of variance (ANOVA) model. The terms in the model will be subject, period and treatment. Subject and period will be fitted as random effects, and treatment will be fitted as a fixed effect. Carryover will also be explored. Following the ANOVA analysis, least squares (LS) means for each treatment will be exponentiated to give LS geometric means for each treatment on the original scale. Differences between treatment LS means (on the ln scale) together with corresponding 2-sided 80% confidence intervals will be derived from the ANOVA model.

For Cohort 2, dose response modelling techniques will be used to explore the dose response relationship for PF-00446687 across the efficacy endpoints.

The remaining efficacy endpoints (arousal/desire questions, time to onset of erections and diary endpoints) will be summarised by treatment.

Safety Analysis

Laboratory and other safety data will be subject to clinical review and tabulation.

Interim Analysis

Data from Cohort 1 will be reviewed prior to the start of Cohort 2 to enable appropriate doses to be chosen for Cohort 2. If PF-00446687 has not demonstrated a signal with Rigiscan[®] Plus in Cohort 1, then Cohort 2 may be cancelled. Data from Cohort 1 will also be used to select the optimal design (including doses) of Cohort 2.

SCHEDULE OF ACTIVITIES

	Screen	Period 1	Period 2	Period 3	Period 4	Follow-up
Written Informed Consent	•					
Demographics	•					
Medical History	•					
IIEF	•					
ECG	•					•
Laboratory Safety	•					•
Physical Examination	•	• ¹	• ¹	• ¹	• ¹	•
Familiarisation with VSS and Rigiscan [®]	•					
Blood pressure/pulse rate	• ³	• ²	• ²	• ²	• ²	• ²
Diary (take home and complete)	•	•	•	•	•	
Urine Drugs of Abuse	•	•	•	•	•	
Breath alcohol		•	•	•	•	
Dosing		•	•	•	•	
VSS and non-VSS stimulation		•	•	•	•	
Plethsmography		•	•	•	•	
PK sample		• ⁵	• ⁵	• ⁵	• ⁵	
PD sample (AgRP)		• ¹	• ¹	• ¹	• ¹	
Sexual Interest and Arousal Questionnaire		• ⁴	• ⁴	• ⁴	• ⁴	• ⁴
Concomitant treatment/ non-drug treatment	•	•	•	•	•	•
Adverse Events		•	•	•	•	•

¹. Clinic days: Prior to dosing and 5 hours post-dose upon completion of final DVD segment.

². Clinic days: Prior to dosing and prior to discharge after resting 5 minutes supine.

³. After resting 5 minutes supine.

⁴. Clinic days: Pre-dose and after each of the DVD segments.

⁵. Clinic days: Prior to dosing and 5 hours post-dose upon completion of final DVD segment.

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1. INTRODUCTION

1.1. Indication

Male erectile dysfunction (MED).

1.2. Background

MED is a very prevalent condition and has a significant impact on quality of life, with subjects commonly reporting increased anxiety, loss of self-esteem, lack of self-confidence, tension and difficulty in relationships with their partner.

PF-00446687 is a potent and selective prototype melanocortin MC4 receptor agonist, in development for the treatment of female sexual dysfunction (FSD) and MED. There is no precedent for a selective agonist of the MC4 receptor sub-type to treat MED or FSD, however there is clinical precedent for treating both MED (Phase 2b) and FSD (Phase 2a) with non-selective MC receptor agonists. Efficacy in these studies has been limited by poor toleration (significant nausea and vomiting). Pre-clinical data support the hypothesis that selective MC4 agonism could improve the therapeutic window.

1.2.1. Information on PF-00446687

PF-00446687 behaves as a full agonist at the MC4 receptor. It is highly selective for the MC4 receptor with >60-fold functional selectivity over human recombinant MC1, MC3, and MC5 receptors. PF-00446687 has little interaction with physiologically important receptors, binding sites, enzymes, or ion channels at relevant concentrations (up to 10 to 100 μ M). PF-00446687 combines significant solubility and membrane permeability, resulting in complete CNS penetration.

For information regarding the safety pharmacology and toxicology data refer to the Investigator's Brochure.

1.2.1.1. Preclinical efficacy data

PF-00446687 has been evaluated in three *in vivo* pharmacology models to underwrite the confidence in rationale that a centrally acting selective MC4 agonist will be effective in the treatment of female and male sexual dysfunction.

PF-00446687 has been studied in a conscious female rat model of proceptive sexual behaviour wherein it significantly increased sexual proceptive behaviour when compared with vehicle-control animals, at 1 μ g/kg subcutaneously (SC) ($p < 0.01$). Furthermore, PF-00446687, 1 μ g/kg SC did not cause an increase in female proceptivity in the presence of a MC3-MC4 antagonist.

In a conscious rat telemetry model of erection, PF-00446687 (0.1-100 μ g/kg SC) caused a dose-dependent increase in the number of erections observed, with the maximal effect observed at 1 μ g/kg SC; the NOEL was 0.1 μ g/kg SC.

1.2.1.2. Clinical experience

PF-00446687 has been evaluated in 2 completed clinical Studies: A8361001 and A8361002.

In Study A8361001, the pharmacokinetics, pharmacodynamics, safety and toleration of PF-00446687 were determined across a wide sublingual dose range (0.3 to 195 mg) and following oral administration at 32.5 and 195 mg in 16 healthy male subjects. This was a randomised, double-blind, third party open, placebo-controlled, crossover, single dose escalation study.

Following sublingual dosing, peak plasma concentrations were achieved within 2 to 8 hours, exposure increased supra-proportionally with increasing dose (<2-fold relative to dose), and terminal half-life was approximately 12 hours across the entire dose range. Following oral dosing, exposure was similar to that achieved for sublingual dosing at comparable dose levels. Urinary excretion was negligible with <2.5% dose excreted as parent over 48 hours after dosing. There were no discernible differences between PF-00446687 195 mg and placebo for any of the pharmacodynamic markers evaluated (thyroid stimulating hormone, lutenising hormone, follicle stimulating hormone, growth hormone and prolactin). PF-00446687 was well tolerated in Study A8361001 upon single dose administration. There were no deaths, serious or severe adverse events or discontinuations due to adverse events reported in this study and all events had resolved before the end of the study. One subject was temporarily discontinued from the study due to elevated serum enzymes caused by excessive exercise. There were no clinically relevant changes in any of the safety parameters.

A8361002 is a recently completed study to assess the pharmacodynamic effect of a single oral solution dose of PF-00446687 (3 to 200 mg) on penile erections in 48 healthy male volunteers. Erectile activity was monitored using the penile plethysmography Rigiscan[®] Plus methodology whilst watching sequences of erotic and nonerotic DVD material. PF-00446687 was well tolerated in this study. Compared with placebo, a modest effect of PF-00446687 200 mg on erectile activity was observed during the visual sexual stimulation of similar magnitude to that of a PDE5i control. Furthermore, a substantial effect on erectile function was observed in the periods without erotic stimulation, supporting a central mechanism of action for this molecule.

1.3. Rationale

1.3.1. Rationale for Study

Pre-clinical male and female data provide evidence that PF-00446687 may have pro-sexual activity in humans. This is supported by data from the clinical Study A8361002. This study will investigate these effects in MED patients.

Sildenafil is a potent, selective competitive inhibitor of cGMP specific, type 5 PDE, the predominant PDE of the human corpus cavernosum. Sildenafil enhances relaxation of the penile corpus cavernosum induced by nitric oxide-mediated non-adrenergic non-cholinergic

and cholinergic neurotransmission and improves penile erection in MED patients. Sildenafil will be used as a positive control.

Penile plethysmography Rigiscan[®] Plus methodology is an established technique for determining the efficacy of pro-erectile therapies in patients with MED. This technique has been used to determine the effect of phosphodiesterase Type 5 inhibitors, apomorphine, and experimental agents such as the melanocortin receptor agonists Melanotan II and PT-141.

This study will investigate the efficacy of PF-00446687 in MED.

1.3.2. Rationale for dose selection

PF-00446687 200 mg will be used for Cohort 1 in this study. This dose has shown to be safe and well tolerated in healthy male volunteers, showing a modest effect on erectile function. Doses for Cohort 2 will be determined upon completion of Cohort 1, following the interim analysis.

Sildenafil 100 mg will be used as a positive control in this study. This dose has proven to be safe and well tolerated with a good response rate in this population.

2. STUDY OBJECTIVES AND ENDPOINTS

To confirm the efficacy of single oral doses of PF-00446687 200 mg in improving penile erectile activity, utilizing 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 questionnaire following single doses of PF-00446687.

To determine the safety and toleration of PF-00446687 in this population.

To assess PK after single doses of PF-00446687 and sildenafil in this population.

To assess Agouti Related Protein (AgRP) levels in this population.

3. STUDY DESIGN

This is a two-cohort study. Up to 16 subjects will complete Cohort 1 and up to 32 subjects will complete Cohort 2.

Cohort 1 will consist of a randomized, double-blind, double-dummy, placebo-controlled, 4-way crossover design. During two of the four study visits, subjects will receive a single dose of PF-00446687 200 mg. During the remaining study visits, subjects will receive sildenafil 100 mg (the positive control) and placebo. Subjects will attend screening and

familiarization visits (which may be combined) and 4 study visits, with a minimum of 7 days washout between study periods.

Data from Cohort 1 will be analyzed during the interval between cohorts to determine if Cohort 2 will proceed and the final design details and dose selection for Cohort 2.

Cohort 2 will consist of a randomized, double-blind, placebo-controlled, 4-way crossover design, assessing dose response of PF-00446687. Sildenafil may or may not be used as a positive control in Cohort 2 (dependent on the outcome of the interim analysis from Cohort 1). Actual doses of PF-00446687 will be determined after the interim analysis but will not exceed 200 mg. Doses may be repeated. The final design (may be complete or incomplete block design) will be determined after analysis of Cohort 1. Should sildenafil be used in Cohort 2, the study will become double-dummy.

At the screening visit, the subjects' suitability for the study will be assessed. At the screening visit, in addition to standard medical assessment procedures (which should include a genital examination), subjects will also complete the International Index of Erectile Function (IIEF) questionnaire to determine severity of erectile dysfunction and more general sexual response and will be familiarized with the equipment and the DVD material that will be used at each study visit. They will be given a paper Diary of Sexual Events to complete in the 7 days leading up to study visit 1.

During each of the study visits, subjects will undergo a brief physical examination, including supine blood pressure and pulse rate. A breath alcohol and a urine 'drugs of abuse' test will be performed prior to the plethysmography. This must be negative. Concomitant medication history will be documented. Adverse event information will be collected prior to, and post dose during all study visits. A blood sample for AgRP will be taken prior to dosing. A urinalysis will also be done. The diary will be reviewed for sexual events from screening or previous study period to ensure it is completed correctly. A snack meal will be provided.

The penile plethysmograph (Rigiscan) will be applied according to the manufacturer's instructions. After the first 15 minutes of recording, the Rigiscan device will be switched off and re-initialised. The Rigiscan will thereafter be re-initialised and recording will be continuous from 30 minutes prior to dosing until 5 hours after dosing. Subjects will be dosed 30 minutes after the plethysmography has started recording for the second time. The subject should be dosed in a sitting position. Following dosing, subjects should not lie down for at least one hour, although being semi-recumbent is permissible. Sequences of neutral and sexually explicit DVD material and questionnaires of sexual interest and desire will be administered according to following sequence:

Questionnaire 1 (without film specific question)



Apply Rigiscan



15 mins of calibration (no DVD material)



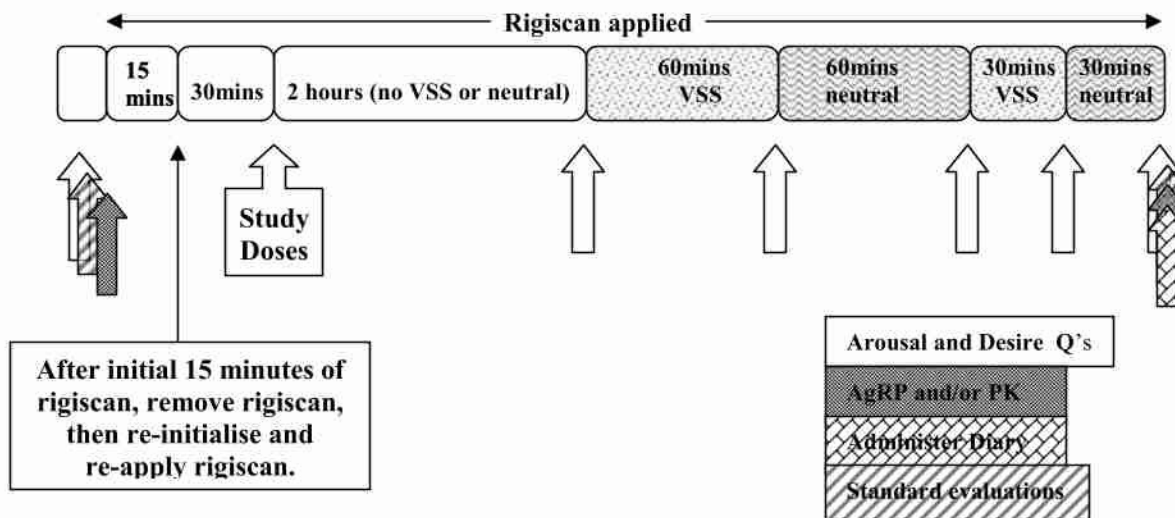
Switch off Rigiscan and re-initialise machine

↓
Apply Rigiscan for the second time
↓
30 mins run-in (no DVD material)
↓
Dosing
↓
120 minutes (no DVD material) Pre-VSS-1
↓
Questionnaire 2
↓
60 mins of Visual Sexual Stimulation (VSS-1)
↓
Questionnaire 3
↓
60 mins of neutral (documentary) DVD (Neutral-1)
↓
Questionnaire 4
↓
30 mins of Visual Sexual Stimulation (VSS-2)
↓
Questionnaire 5
↓
30 mins of neutral (documentary) DVD (Neutral-2)
↓
Questionnaire 6

At 5 hours post-dose, following completion of the penile plethysmography session, blood samples for PK (sildenafil and PF-00446687) and AgRP will be taken. A brief physical examination, including supine blood pressure, will be performed. Any adverse events will be noted. A meal will be offered. If the investigator has any clinical concerns the subject will be monitored and appropriately managed. A new diary will be handed to the subject. Subjects will be instructed to complete the diary every day, starting the day of dosing (Day 1), recording details of their sexual activity over the next 7 days.

A physical examination, supine blood pressure and pulse rate and laboratory safety tests (haematology, clinical chemistry and urinalysis) will be performed 7-14 days following the final study period.

Figure 1. Study Day Procedures



4. SUBJECT SELECTION

This study can fulfil its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Male subjects aged 18-65 years.
2. Subjects who have given written informed consent to participate in the study.
3. Subjects must be in a heterosexual stable relationship for at least the last 6 months.
4. Subjects with erectile dysfunction of at least six months duration prior to entering the study. Erectile dysfunction is defined as "the inability to attain and/or maintain penile erection sufficient for satisfactory performance". [1]
5. Subjects with moderate to severe (6-16) erectile dysfunction as classified on the International Index of Erectile Function (IIEF).
6. Subjects who, in the opinion of the investigator, are known responders to PDE5i's, such as subjects with a current or recent (within 6 months) history of successful PDE5i use.
7. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other trial procedures.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are either known non-responders to, or unlikely to respond to treatment with either MC4 agonists or PDE5i's. This includes subjects who are diabetic, subjects with significant neurological disease, spinal cord injury, multiple sclerosis, or previous pelvic surgery including radical and nerve sparing prostatectomy.
2. Subjects with any clinically significant abnormality, following review of pre-study laboratory data and after a full physical examination.
3. Subjects with a history of significant cardiac disease, particularly moderate or severe cardiac failure, unstable angina or recent myocardial infarction, stroke or life-threatening arrhythmia within the previous 6 months.
4. Subjects with a history of syncope or cardiac conduction abnormality (including paroxysmal brady or tachyarrhythmias).
5. Subjects who suffer from hypo- or hypertension (treated as well as untreated) or have a resting supine blood pressure below 90/50 mm Hg or above 170/110 or who show a postural drop in either systolic blood pressure of >20 mm Hg or diastolic blood pressure of >10 mm Hg at screening.
6. Subjects who are currently receiving vasoactive medication, such as (but not limited to) α -blockers, β -blockers, calcium antagonists.
7. Subjects who are receiving drugs known to inhibit CYP3A4, such as ketoconazole (systemic), erythromycin, cimetidine, clarithromycin, fluvoxamine, itraconazole (systemic), voriconazole, protease inhibitors.
8. Subjects with any clinically significant haematological, renal or hepatic abnormality.
9. Subjects with major psychiatric disorders and those who have received treatment for any major psychiatric disorder (eg, psychosis or hospitalization due to major depression) within the past 12 months.
10. Subjects who have received any experimental (ie, non-approved) drug within the past four months (prior to the first dosing day of the study).
11. Subjects who drink more than 21 units of alcohol per week. (1 unit = 285 mL of beer or 25 mL of spirits or 125 mL of wine).
12. Subjects with a history of controlled substance abuse within the past 2 years.
13. Subjects who, in the opinion of the principal investigator, have any medical or psychological condition or social circumstances which would impair their ability to

participate reliably in the study, or who may increase the risk to themselves or others by participating.

14. Subjects who, in the opinion of the investigator, are not likely to complete the study for whatever reason.
15. Subjects with a history of hypersensitivity to study drug and its excipients or known allergy to sildenafil and/or MC agonists.
16. Subjects with other forms of sexual dysfunction (eg, retrograde ejaculation, an ejaculation, painful ejaculation, premature ejaculation, hypoactive sexual desire and inhibited or absent orgasm).
17. Subjects with Peyrone's disease.
18. Subjects with evidence or history of seizure disorder, clinically significant haematological, renal, hepatic, psychiatric, neurologic or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing).
19. History of febrile illness within 5 days prior to the first dose.
20. Subjects with any condition possibly affecting drug absorption (eg, gastrectomy).
21. Blood donation of approximately 1 pint (500 mL) within 56 days prior to dosing and subjects intending to donate during the study.
22. Subjects with a 12-lead ECG demonstrating QTc >450 msec at screening.

Criteria specific to Sildenafil:

23. Subjects who are prescribed and/or taking medication which is contraindicated or cautioned with concomitant intake of PDE5 inhibitors, such as nitrates or nitric oxide donors in any form (oral, sublingual, buccal, inhalational or aerosols), cimetidine, CYP3A4 inhibitors, such as erythromycin, ketoconazole and protease inhibitors.
24. Subjects with retinitis pigmentosa.
25. Subjects who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5i exposure.
26. Subjects with congestive cardiac failure or coronary artery disease causing unstable angina, recent history of myocardial infarction or stroke.

4.3. Randomization Criteria

Sixteen subjects will complete Cohort 1 and up to 32 subjects will complete Cohort 2. It is envisaged that up to 3 sites will actively recruit into Cohorts 1 and 2. Each site should

complete approximately 5 subjects each in Cohort 1 and between 8 and 12 in Cohort 2. Enrolment will be competitive and co-ordinated by Pfizer. Each subject will be assigned to a sequence of treatment administrations, by means of a computer generated, pseudo random code.

The treatments to be administered in Cohort 1 are:

PF-00446687 200 mg with sildenafil placebo
Repeat PF-00446687 200 mg with sildenafil placebo
Sildenafil 100 mg with PF-00446687 placebo
PF-00446687 placebo with sildenafil placebo

The treatments to be administered in Cohort 2 will be determined upon analysis of data from Cohort 1. This may or may not include sildenafil 100 mg. The doses administered of PF-00446687 in Cohort 2 will not exceed 200 mg. No more than 4 study visits will take place in Cohort 2. One of the study visits will be placebo.

4.4. Life Style Guidelines

Subjects should refrain from sexual activities (eg, sexual intercourse and masturbation) in the 24 hours prior to each study period. Subjects should attend the clinic having eaten breakfast.

Subjects should also refrain from consuming grapefruit or grapefruit juice for the duration of the study.

Subjects who have a partner of childbearing potential must use or ensure that their partner uses a barrier method of contraception for the duration of the trial and for 3 months after study completion.

5. TREATMENTS

5.1. Allocation to Treatment

Cohort 1 will be a Williams design with 4 treatments (A, B, C, D) where treatment D has been replaced with a repeat of treatment C (Table 1).

Table 1. Randomisation Sequence

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	C	B	C
Sequence 2	B	A	C	C
Sequence 3	C	B	C	A
Sequence 4	C	C	A	B

Treatment C represents PF-00446687 200 mg and A and B are placebo and sildenafil 100 mg in some order.

5.2. Breaking the Blind

All study sites will be instructed in the method for blind breaking. Blinding codes should only be broken in emergency situations for reasons of subject safety. The investigator will be provided with sealed copies of the randomisations which allow the investigator to break the treatment code for an individual subject. When the investigator, in an emergency, requires immediately to identify the study treatment for a given subject, he/she must record in detail the reason on the case report form and date and sign the appropriate section of the sealed randomizations as soon as possible after the event. In no other instance should the code be broken without prior consultation with the Pfizer clinician. Any data generated after the treatment code has been broken for a given subject may be excluded from analysis unless they have a bearing on the safety of the drug.

5.3. Drug Supplies

PF-00446687 and placebo will be provided as bulk powders for oral solution. Individual doses will be presented to the subjects in a suitable vessel for oral administration.

The positive comparator (sildenafil citrate 100mg tablets) and blinded placebo tablets for the positive comparator will be supplied to the clinical unit as bulk tablets.

5.3.1. Formulation and Packaging

PF-00446687 and placebo will be provided by Pfizer Ltd as bulk powders for preparation of oral dosing solutions at the clinical unit. Sildenafil citrate 100mg and blinded placebo tablets will be provided by Pfizer Ltd as bulk tablets to be dispensed at the clinical unit.

5.3.2. Preparation and Dispensing

PF-00446687 and placebo oral dosing solutions will be prepared in the Unit by an appropriately qualified person. Details of dose preparation will be given in a separate Extemporaneous Dispensing Record (EDR). Sildenafil citrate 100mg and blinded placebo tablets will be dispensed in the Unit by an appropriately qualified person.

5.3.3. Administration

On Day 1 of each study period in Cohort 1, subjects will be asked to drink a solution containing either PF-00446687 or placebo for PF-00446687 immediately followed by a tablet of sildenafil 100 mg or placebo tablet.

PF-00446687 will be administered dissolved in an appropriate volume dependant on dose level. The empty container will be rinsed with ambient temperature water. The total volume

of liquid the subject will be required to drink (including rinsings) will not exceed 240 mL. Subjects will take the tablet whole with the rinsing solution.

On Day 1 of each study period in Cohort 2 a similar procedure will be followed to that in Cohort 1. If sildenafil is not part of the final design of Cohort 2 then no tablets will be taken with the rinsing solution.

5.3.4. Compliance

Trial treatment will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing to assure the trial medication was taken.

5.4. Drug Storage and Drug Accountability

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area, under recommended storage conditions (as detailed in the Extemporaneous Dispensing Record) and in accordance with applicable regulatory requirements.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s). Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

At the end of the trial, all unused drug supplies will be checked by the CRA and/or pharmacist. Unless otherwise authorised by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subject must be returned to Pfizer.

5.5. Concomitant Medication(s)

Subjects receiving treatment for MED such as PDE5i's dopamine agonists, intracavernosal therapy or topical transurethral alprostadil or herbal therapies may be included, provided they remain off therapy for 2 weeks prior to first dose and for the duration of the study.

Subjects who are receiving drugs known to inhibit CYP3A4, such as ketoconazole (systemic), erythromycin, cimetidine, clarithromycin, fluvoxamine, itraconazole (systemic), voriconazole, protease inhibitors should be excluded.

At each visit the investigator will obtain any information about concomitant illnesses and any therapeutic intervention eg, drug therapy, surgery, etc.

5.6. Rescue Therapy

No mechanistically specific antagonists for PF-00446687 or sildenafil are available and standard supportive measures should be used in the case of excessive pharmacological effect.

5.7. Availability of Treatment upon completion of Trial

Sildenafil is a licensed product and will be available on prescription. PF-00446687 is an experimental compound that will not be available on completion of this trial.

6. STUDY PROCEDURES

For further details of procedures on the study, see Assessments Section 7.

6.1. Screening

Screening can occur within 28 days prior to the administration of the trial medication to confirm that the subject meets the trial selection criteria.

- Written informed consent will be obtained before any study related procedures commences.
- Subjects will undergo medical history documentation, history of concomitant medication and alcohol usage.
- Completion of the International Index of Erectile Function (IIEF) questionnaire (see Appendix 1).
- A full physical examination will be done. Body weight and height will be recorded in the CRF.
- Supine and standing blood pressure and pulse rate will be measured.
- A 12-lead ECG recording will be done.
- A urine sample for drugs of abuse test will be performed.
- Blood will be drawn for haematology, and biochemistry (particular tests described in Section 7.2.4), the results of which will be reviewed prior to inclusion of the subject in the study. Provided the results of the tests are satisfactory and that all the entrance criteria are fulfilled the subject may enter the study. Urinalysis will also be done as part of the laboratory safety tests.
- In order for the subject to be confident and at ease with the penile plethysmography (Rigiscan) technique and the nature of the audio/visual sexual stimulation, he will be shown the equipment and 5 minutes of the VSS.
- Subjects will also be given a Diary of Sexual Events to complete daily in the 7 days leading up to the first study period (see Appendix 3).

6.2. Study Period

6.2.1. Pre-dosing

- A light snack (for example two crackers or biscuits or 2 slices of toast) will be allowed up to 2 hours prior to dosing. Following the light snack at the clinical unit no food will be consumed until after the assessments for the study period are complete. Fluid will be restricted from 2 hours prior to dosing to after the assessments for the study period have been completed.
- Collect and review Diary of Sexual Events from screening or previous study period to ensure it is completed correctly.
- A concomitant medication history will be documented.
- Adverse event information will be collected prior and post dosing in study periods 2, 3 and 4.
- Subjects will undergo a brief physical examination.
- Supine blood pressure and pulse rate will be taken.
- A breath alcohol and a urine drugs of abuse test will be performed prior to the plethysmography.
- Subjects will complete Sexual Interest and Arousal Questionnaire 1 (see Appendix 2).
- The penile plethysmograph (Rigiscan) will be applied according to the manufacturer's instructions. After the initial 15 minutes of recording it will be switched off, re-initialised and re-started. Recording will be continuous from 30 minutes prior to dosing (see Section 7.1.1).
- Subjects will then be dosed 30 minutes after the plethysmography has been re-initialised and started recording. The subject should be dosed in a sitting position. Following dosing subjects should not lie down for at least one hour but being semi-recumbent is permissible.

6.2.2. Post -dosing

- The first two hours following dosing the subjects will not watch any DVD material.
- Following the two hours of no DVD material Sexual Interest and Arousal Questionnaire 2 will be completed.
- Two hours after dosing subjects will be subjected to the first session of 60 minutes of visual sexual stimulation (VSS-1).
- Following the VSS-1, Sexual Interest and Arousal Questionnaire 3 will be completed.
- The first 60 minute neutral video session will follow (neutral-1).
- At the end of neutral-1, Sexual Interest and Arousal Questionnaire 4 will be completed.
- The 30 minute VSS-2 session will follow.

- Sexual Interest and Arousal Questionnaire 5 will be completed.
- The 30 minute neutral-2 session will occur.

6.2.3. Post - Rigiscan

- Completion of Sexual Interest and Arousal Questionnaire 6.
- A supine blood pressure will be taken.
- A blood sample for the analysis of PF-00446687 and sildenafil concentrations (PK) and for AgRP, will be taken.
- A brief physical examination will be done. If the investigator has any clinical concerns he will monitor and appropriately manage the subject.
- Any adverse event will be noted during and after each treatment period.
- Subjects will be given a daily diary to record details of their sexual events for 7 days, counting the day of dosing as day 1 (see Appendix 2).

6.3. Follow-up Visit

A full physical examination, supine blood pressure and pulse rate, a 12-lead ECG, laboratory safety tests (haematology, biochemistry) and urinalysis will be performed 7 to 10 days following the final dose. Adverse events will be monitored and any concomitant medication will be noted.

Collect and review Diary of Sexual Events from the final study period to ensure it is completed correctly.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

7.1. Efficacy

7.1.1. Penile Plethysmography

The penile plethysmography (Rigiscan) will be applied according to the manufacturer's instructions. After the initial 15 minutes of recording, the Rigiscan will be switched off and re-initialised. The Rigiscan will be restarted and recording will be continuous from 30 minutes pre-dose to 5 hours post-dosing.

7.1.2. Questionnaire (Measure of Sexual Interest and Arousal)

Prior to commencing the Rigiscan recording, 2 hours post-dose and after completion of each of the DVD segments (a total of 6 times during each study period). The questionnaire is presented in Appendix 2.

7.1.3. Diary Assessment of Sexual Activity

Prior to study period 1 and after each of the 4 study periods. The diary is presented in Appendix 3.

7.2. Safety

7.2.1. Blood pressure/Pulse rate measurements

(Screening, Study periods: Pre-dose and Discharge, Follow-up)

At screening, supine and standing blood pressure and pulse rate measurements will be recorded at screening after resting supine for 5 minutes prior to the measurements being taken, then seated for 2 minutes before standing up and standing up for a further 2 minutes, after which a standing measurement will be taken. During study periods and follow-up, only supine blood pressure measurements will be recorded.

7.2.2. Electrocardiogram

(Screening, Follow-up)

A 12-lead ECG will be recorded after resting for 5 minutes supine.

7.2.3. Adverse events

Information on adverse events (AE) occurring will be recorded at each visit to the clinic. Information on AEs will be obtained using non-leading questioning.

7.2.4. Laboratory safety tests

(Screening and Follow-up)

Haematology: haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), red blood cell (RBC) count, platelet, white blood cell (WBC) count including differential (% and

absolute).

Serum biochemistry: alanine transaminase (ALT), albumin, alkaline phosphatase (AP), aspartate transaminase (AST), calcium, creatinine, gamma glutamyl transpeptidase (GGT), magnesium, potassium, chloride, sodium, bicarbonate, total bilirubin, total protein, urea.

Urinalysis: standard dipstick test for blood, glucose, ketones, pH and protein.

7.2.5. Urine drug screen and breath alcohol Test

Urine drug screen is to be carried out at the screening visit and on admission to the clinic at each study period. The urine drug screen (Triage kits, provided by Pfizer) will include tests for cocaine, cannabinoids, opiates, barbiturates, benzodiazepines, methadone and amphetamines at screening. Breath alcohol testing will be performed on admission to the clinic at each study period. Results of each test have to be negative.

7.2.6. Physical Examination

Subjects will have a full physical examination (to include peripheral and central nervous system, respiratory system, cardiovascular system, ears, nose, throat, thyroid gland, skin, abdomen and genitals) at screening, and at the follow-up visit. On admission to the clinic before each study period and before discharge from the clinic of each period, subjects will have a brief physical examination, which will consist of an examination of the cardiovascular, the respiratory, the abdomen and the skin.

7.3. Pharmacokinetic sampling

Blood samples (up to 6 mL) to provide 2 mL plasma for pharmacokinetic analysis for PF-00446687 or sildenafil (as appropriate) will be collected into appropriately labelled tubes containing lithium heparin. Samples will be taken 5 hours post dose during each study period. All efforts will be made to obtain the pharmacokinetic sample at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the trial.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C within 1 hour of collection. The plasma will be stored in appropriately labelled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection. Samples will be analysed using a validated analytical method in compliance with Pfizer standard operating procedures.

7.4. Pharmacodynamic Sampling

Blood samples (2.5 mL) to provide 2 aliquots of 300 µl of plasma for analysis of AgRP will be collected into appropriately labelled tubes containing lithium heparin at pre-dose and at 5 hours post-dose during each study period. All efforts will be made to obtain the

pharmacodynamic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool. The shipment address and assay lab contact information will be provided to the investigator site.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C within 1 hour of collection. The plasma will be stored in appropriately labelled screw-capped polypropylene tubes at approximately -20°C.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Samples may or may not be analyzed dependent on the outcome of a multiple dose study. If samples are to be analyzed, this will be performed at the end of the study.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Reporting Period

Serious adverse events require immediate notification to Pfizer or its designated representative beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings.
- Clinically significant symptoms and signs.
- Changes in physical examination findings.
- Hypersensitivity.
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose.
- Drug withdrawal.
- Drug abuse.
- Drug misuse.
- Drug interactions.
- Drug dependency.
- Extravasation.
- Exposure in utero.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly/birth defect.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities.
- Hospice facilities.
- Respite care (eg, caregiver relief).
- Skilled nursing facilities.
- Nursing homes.
- Routine emergency room admissions.
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Social admission (eg, subject has no place to sleep).
- Administrative admission (eg, for yearly physical exam).
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery).
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure In Utero

For investigational products within clinical trials and for marketed products, an exposure in-utero (EIU) occurs if:

1. a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure).
2. a male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial subject or trial subject's partner becomes or is found to be pregnant during the trial subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted foetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The “normality” of an aborted foetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should be reported.

8.10. Withdrawal Due to Adverse Events (See also on Subject Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Pfizer.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

Simulations have shown that repeating PF-00446687 200 mg within each subject is expected to increase power from 67% to 83% for 16 subjects. Power is defined as the percentage of times a p-value of less than 5% was seen in the simulated trials when testing the null hypothesis.

H0: PF-00446687 200 mg = Placebo

Against the alternative hypothesis

H1: PF-00446687 200 mg $\neq$ Placebo

These results are based on the duration of $\geq 60\%$ rigidity during VSS, normalised to 60 minutes of VSS. The simulations were based on the following assumptions about underlying values:

1. Duration of $\geq 60\%$ rigidity for placebo = 10.2 minutes
2. Duration of $\geq 60\%$ rigidity for PF-00446687 200 mg = 21.5 minutes
3. Within subject standard deviation = 10.0 minutes

The precision in estimating the difference between PF-00446687 200 mg and Placebo (PF-00446687 – Placebo) for this endpoint is expected to be 4.5 to 14.0 minutes using a 2-sided 90% confidence interval, under the above assumptions (where the difference is 11.3 minutes). Without the repeated period of PF-00446687 200 mg, the expected precision was 2.9 to 15.6 minutes.

The above assumptions represent an expected 2.1 fold increase for PF-00446687 200 mg over Placebo (PF-00446687 200 mg / Placebo) and the precision for estimating the fold increase is expected to be 1.4 to 2.4. This result includes the repeated period for PF-00446687 200 mg and is based on a 2-sided 90% confidence interval. The corresponding result for a 2-sided 80% confidence interval is 1.5 to 2.3.

Duration of $\geq 60\%$ rigidity for Sildenafil is expected to be 24.7 minutes during VSS, normalised to 60 minutes. This represents an expected difference from Placebo of 14.5 minutes (Sildenafil 100 mg – Placebo) and corresponds to a fold increase (Sildenafil 100 mg / Placebo) of 2.4.

These assumptions are based on data from Pfizer Studies A8361002 and A7771002. [2, 3]

The sample size for Cohort 2 is not expected to exceed 32 subjects, and will be determined (and justified) following review of Cohort 1 data.

9.2. Efficacy Analysis

Each cohort will be analysed separately.

9.2.1. Analysis of VSS Efficacy Endpoints

For Cohort 1, the VSS endpoints will be analysed on the natural log scale (ln) using a mixed effects analysis of variance (ANOVA) model. The terms in the model will be subject, period and treatment. Subject and period will be fitted as random effects, and treatment will be fitted as a fixed effect. Carryover will also be explored. Following the ANOVA analysis, least squares (LS) means for each treatment will be exponentiated to give LS geometric means for each treatment on the original scale. Differences between treatment LS means (on the ln scale) together with corresponding 2-sided 80% confidence intervals will be derived from the ANOVA model. Contrasts (differences) of interest are:

PF-00446687 200 mg versus placebo.

Sildenafil 100 mg versus placebo.

These differences will also be exponentiated to give the ratio between geometric means (each treatment versus placebo) together with corresponding 80% confidence intervals for the ratios. No p-values will be presented.

For Cohort 2, dose response modelling techniques will be used to explore the dose response relationship for PF-00446687 across the efficacy endpoints.

9.2.2. Analysis of Non-VSS Efficacy Endpoints

The remaining efficacy endpoints (arousal/desire questions, time to onset of erections and diary endpoints) will be summarised by treatment.

9.3. Analysis of Other Endpoints

PK and AgRP samples (if analyzed) will be summarized. For AgRP, change at 5 hours post-dose relative to pre-dose measurement will be calculated and summarized.

9.4. Safety Analysis

Laboratory and other safety data will be subject to clinical review and tabulation.

9.5. Interim Analysis

Data from Cohort 1 will be reviewed prior to the start of Cohort 2 to enable appropriate doses to be chosen for Cohort 2. If PF-00446687 has not demonstrated a signal with Rigiscan® Plus in Cohort 1, then Cohort 2 may be cancelled. Data from Cohort 1 will also be used to select the optimal design (including doses) of Cohort 2.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms / Electronic Data Record

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the accuracy and authenticity of all clinical, safety, laboratory data entered on the CRFs. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, Pfizer should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg,

advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing within 5 working days after the implementation.

12.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by Pfizer and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use. The investigator will retain the original of each subject's signed consent form.

13. DEFINITION OF END OF TRIAL

13.1. End of Study in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Study Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-00446687 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects within six months. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through postings on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on **www.clinicaltrials.gov**, (ClinicalTrials.gov) regardless of the reason for registration, **OR**
- All other studies for which the results have scientific or medical importance as determined by Pfizer.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed.

- For studies involving products already approved in any country and for studies that do not involve a Pfizer product, Pfizer posts results within one year after study completion, defined as last subject, last visit (LSLV).
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within one year after the first regulatory approval of the product.
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results of already-completed studies within one year after such discontinuation.

Pfizer's posting on ClinicalStudyResults.org includes the following elements:

- Protocol title, study phase, and indication.

- A link to approved product labelling, if applicable.
- The synopsis of study results.
- Citations of known study publications.
- Legal disclaimer.

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 *Clinical Study Report (CSR) Synopsis*. If posting of study results to ClinicalStudyResults.org jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has issued or two years have elapsed, whichever occurs first.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favourable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre trial, Investigator agrees that the first publication is to be a joint publication covering all centres. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of trial results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In the above section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Impotence – NIH Consensus Conference. JAMA 1993;270:83-90.
2. Pfizer A8361002 Clinical Protocol.
3. Pfizer A7771002 Clinical Protocol.

Appendix 1. IIEF

Over the past 4 weeks:

1. How often were you able to have an erection during sexual activity?

- 0 = no sexual activity
- 1 = almost never/ never
- 2 = a few times (much less than half the time)
- 3 = sometimes (about half the time)
- 4 = most times (much more than half the time)
- 5 = almost always/ always

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?

- 0 = no sexual activity
- 1 = almost never/ never
- 2 = a few times (much less than half the time)
- 3 = sometimes (about half the time)
- 4 = most times (much more than half the time)
- 5 = almost always/ always

3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

- 0 = did not attempt intercourse
- 1 = almost never/ never
- 2 = a few times (much less than half the time)
- 3 = sometimes (about half the time)
- 4 = most times (much more than half the time)
- 5 = almost always/ always

4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

- 0 = did not attempt intercourse
- 1 = almost never/ never
- 2 = a few times (much less than half the time)
- 3 = sometimes (about half the time)
- 4 = most times (much more than half the time)
- 5 = almost always/ always

5. During sexual intercourse, how difficult was it to maintain your erection to complete intercourse?

- 0 = did not attempt intercourse
- 1 = extremely difficult
- 2 = very difficult
- 3 = difficult
- 4 = slightly difficult
- 5 = not difficult

6. Over the past 4 weeks how many times have you attempted sexual intercourse?

- 0 = no attempts
- 1 = 1-2 attempts
- 2 = 3-4 attempts
- 3 = 5-6 attempts
- 4 = 7-10 attempts
- 5 = 11 + attempts

7. Over the past 4 weeks when you attempted sexual intercourse how often was it satisfactory for you?

- 0 = did not attempt intercourse
- 1 = almost always or always
- 2 = most times (much more than half the time)
- 3 = sometimes (about half the time)
- 4 = a few times (much less than half the time)
- 5 = almost never or never

8. Over the past 4 weeks how much have you enjoyed sexual intercourse?

- 0 = no intercourse
- 1 = very highly enjoyable
- 2 = highly enjoyable
- 3 = fairly enjoyable
- 4 = not very enjoyable
- 5 = not enjoyable

9. Over the past 4 weeks when you had sexual stimulation or intercourse how often did you ejaculate?

- 0 = no sexual stimulation or intercourse
- 1 = almost always or always
- 2 = most times (much more than half the time)
- 3 = sometimes (about half the time)
- 4 = a few times (much less than half the time)
- 5 = almost never or never

10. Over the past 4 weeks when you had sexual stimulation or intercourse how often did you have the feeling of orgasm with or without ejaculation?

- 0 = no sexual stimulation or intercourse
- 1 = almost always or always
- 2 = most times (much more than half the time)
- 3 = sometimes (about half the time)
- 4 = a few times (much less than half the time)
- 5 = almost never or never

11. Over the past 4 weeks how often have you felt sexual desire?

- 0 = almost always or always
- 1 = most times (much more than half the time)
- 2 = sometimes (about half the time)
- 3 = a few times (much less than half the time)
- 4 = almost never or never

12. Over the past 4 weeks how would you rate your level of sexual desire?

- 0 = very high
- 1 = high
- 2 = moderate
- 3 = low
- 4 = very low or none at all

13. Over the past 4 weeks how satisfied have you been with your overall sex life?

- 0 = very satisfied
- 1 = moderately satisfied
- 2 = about equally satisfied and dissatisfied
- 3 = moderately dissatisfied
- 4 = very dissatisfied

14. Over the past 4 weeks how satisfied have you been with your sexual relationship with your partner?

- 0 = very satisfied
- 1 = moderately satisfied
- 2 = about equally satisfied and dissatisfied
- 3 = moderately dissatisfied
- 4 = very dissatisfied

15. How do you rate your confidence that you could have and keep an erection?

- 1 = very low
- 2 = low
- 3 = moderate
- 4 = high
- 5 = very high

All items should be completed and databased.

Subjects must score between 6 and 16 based upon the sum of items 1 to 5 + item 15 to be included in the study:

- 26-30 = No ED
- 22-25 = Mild
- 17-21 = Mild to moderate
- 11-16 = Moderate
- 6-10 = Severe

Appendix 2. Sexual Interest and Arousal Questionnaire

Please answer the following questions as honestly as possible. Please CIRCLE ONE OPTION ONLY. The answers work on a scale, where 0 is on the low level whereas 6 is the highest level.

1. How would you rate your level of sexual interest at this moment?	0 1 2 3 4 5 6 0 = no sexual interest 6 = extreme sexual interest
2. How strong is your inclination to engage in sexual behaviour by yourself (eg, touching your genitals, masturbation etc)?	0 1 2 3 4 5 6 0 = no inclination 6 = very strong inclination
3. Right now, how easy is it for you to have sexual thoughts and fantasies?	0 1 2 3 4 5 6 0 = not at all easy 6 = very easy
4. Right now, how turned on do you feel?	0 1 2 3 4 5 6 0 = not turned on 6 = extremely turned on
5. Right now, if you were in a romantic/ideal situation with a partner, how strong would your sexual desire be?	0 1 2 3 4 5 6 0 = no desire 6 = very strong desire
6. Right now, if you were in a sexual situation with a partner in your own home, how easy do you think it would be to become fully aroused?	0 1 2 3 4 5 6 0 = not at all easy 6 = very easy
7. IF APPLICABLE How comfortable were you with the content of this film?	0 1 2 3 4 5 6 0 = not at all comfortable 6 = Very comfortable

Appendix 3. Subject Diary of Sexual Events

1. Please indicate how much you have thought about sex/felt interested in being sexual today.	0 1 2 3 4 5 6 7 8 9 10 None at all A very great deal
2. Did you get an erection today?	☐ 0 No erection ☐ 1 Increase in size but not hard ☐ 2 Hard but not hard enough for penetration ☐ 3 Hard enough for penetration but not completely hard) ☐ 4 Completely hard
3. Did you take part in any sexual activity today? Sexual activity includes any activity, which may result in sexual stimulation or pleasure eg, intercourse, caressing, foreplay, masturbation (self-masturbation or your partner masturbating you) and oral sex.	☐ Yes ☐ No
4. Did your sexual activity include sexual intercourse?	☐ Yes ☐ No
5. If yes, did your erection last long enough to complete intercourse?	☐ Yes ☐ No ☐ No erection

Appendix 4. Clinical Protocol Amendment(s)

Current Amendment:

Amendment No.	Date	Country (ies)	Site(s)
1	21 May 2007	All	All

Previous Amendments:

Amendment No.	Date	Country (ies)	Site(s)
None			

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Appendix 4.1. Global Amendment 1

Summary

The MHRA requested that subjects recruited to this study who have a partner of childbearing potential use or that their partner uses a barrier method of contraception.

Reason(s) for Amendment

To ensure that subjects recruited to this study, who have partners of childbearing potential, use or that their partner use a barrier method of contraception.

The protocol sections that were amended are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol. **Bolded text** is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.
- The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Protocol Section(s) Amended

Section 4.4. Life Style Guidelines, Page 19

Change From

Subjects should refrain from sexual activities (eg, sexual intercourse and masturbation) in the 24 hours prior to each study period. Subjects should attend the clinic having eaten breakfast.

Subjects should also refrain from consuming grapefruit or grapefruit juice for the duration of the study.

Subjects who have a partner of childbearing potential must use or ensure that their partner uses a barrier method of contraception for the duration of the trial and for 3 months after study completion.

Change To

Subjects should refrain from sexual activities (eg, sexual intercourse and masturbation) in the 24 hours prior to each study period. Subjects should attend the clinic having eaten breakfast.

Subjects should also refrain from consuming grapefruit or grapefruit juice for the duration of the study.

Subjects who have a partner of childbearing potential must use or ensure that their partner uses a barrier method of contraception for the duration of the trial and for 3 months after study completion.