PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

COMPOUND NUMBER: UK-447,841

PROTOCOL NO.: A5031003

PROTOCOL TITLE: A Two Part Study to a) Investigate the Reproducibility of the Vaginal Photoplethysmography (VPP) Technique in Healthy Pre-Menopausal Volunteers and Subjects Suffering From Female Sexual Arousal Disorder (FSAD) and b) A Randomised Double Blind, Placebo Controlled 4-Way Crossover Study to Investigate the Effect of Single Oral Doses (10, 50 and 400 mg) of UK-447,841 on Vaginal Blood Flow in Pre-Menopausal Subjects Suffering From FSAD

Study Centers: 3 centers 1 each in the United Kingdom, Australia and Norway took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 18 December 2004 to 25 November 2005

Phase of Development: Phase 2A

Study Objectives:

Part A:

Primary Objective:

- To investigate the reproducibility of the vaginal photoplethysmography (VPP) technique in healthy pre-menopausal female volunteers and pre-menopausal subjects suffering from female sexual arousal disorder (FSAD).

Secondary Objective:

- To assess the degree of undesirable artefacts and fluctuations in the vaginal pulse amplitude (VPA) traces;
- To assess the subjective feeling of arousal at baseline and during visual sexual stimulation (VSS);
- To investigate differences in VPA between healthy volunteers and subjects suffering from FSAD.

Part B:

Primary Objective:

- To investigate the effect of single doses of UK-447,841 on vaginal blood flow (VBF) as measured by VPP in pre-menopausal subjects suffering from FSAD.

Secondary Objective:

- To investigate the suitability of this technique in determining sensitivity to change of VBF following dosing with UK-447,841;
- To assess the correlation between changes in VPA and subjective feeling of arousal during sexual arousal;
- To investigate the safety and toleration of single oral doses of UK-447,841 in FSAD subjects;
- To determine plasma concentrations of UK-447,841 in FSAD subjects;
- To assess the effect of UK-447,841 on levels of plasma biomarkers such as vasoactive intestinal peptide (VIP), atrial natriuretic peptide (ANP), big endothelin and cyclic guanosine monophosphate (cGMP).

METHODS

Study Design: This was a 2-part study. Part A investigated the reproducibility of the VPP technique in 8 healthy pre-menopausal volunteers and 8 pre-menopausal subjects suffering from FSAD. Part B was a randomized double-blind, placebo controlled 4-way crossover study to investigate the effect of single oral doses (10, 50 and 400 mg) of UK-447,841 on VBF in 16-24 pre-menopausal subjects suffering from FSAD based upon variability observed in Part A.

During the screening visit, all subjects in both Parts A and B were assessed for FSAD by means of the Female Sexual Function Questionnaire (SFQ) and personal distress question to identify the subjects who had a high probability of suffering from FSAD as well as to confirm the absence of sexual dysfunction in the healthy volunteers. In addition, up to 5 weeks prior to the study start, the subjects underwent a full physical examination (including gynaecological examination). Medical history, concomitant medication information, body weight and height were also obtained. Blood pressure (BP) and pulse rate (PR) were measured after resting for 5 minutes supine and after standing for 2 minutes.

A blood sample for hormonal status and a urine sample for drug screen were also taken. Provided the results of these tests were satisfactory and that all the entrance criteria were fulfilled, the subjects entered the study. FSAD subjects had to undergo an additional semi-structured interview to confirm their diagnosis and exclude hypoactive sexual desire disorder (HSDD). All subjects were familiarized with the VPP technique and nature of the audio/visual sexual stimulation at a familiarization visit as part of the screening visit. Each study period was separated by at least 48 hours and 4 days for subjects in Part A and Part B, respectively.

The visit schedule for Part A and Part B is summarized in Table 1 and Table 2 respectively.

Table 1. Visit Schedule Part A

	Screen	Familiarization (Occurred at Screen)	Period 1	Period 2	Period 3
Written informed consent	X				
Demographics	X				
Medical history	X				
Serum pregnancy test	X				
Laboratory safety	X				
Blood test testosterone/estradiol	X				
ECG	X				
Gynecological examination	X				
Physical examination	X		X[a]	X[a]	X[a]
Blood pressure/pulse rate	X[b]		X[c]	X[c]	X[c]
Urine drugs of abuse	X		X[a]	X[a]	X[a]
Breath alcohol	X		X[a]	X[a]	X[a]
Sexual function questionnaire/distress question	X				
Semi-structured interview FSAD subjects only	X				
Urine pregnancy test	X		X[a]	X[a]	X[a]
Arousal questionnaire	X		X[d]	X[d]	X[d]
VPP with VSS	X	X (5 mins session)	X	X	X
Concomitant treatment/ non-drug treatment	X	X	X	X	X
Adverse events	X	X	X	X	X

ECG = electrocardiogram; FSAD = female sexual arousal disorder; Screen = screening; VPP = vaginal photoplethysmography; VSS = visual sexual stimulation.

a. Prior to VPP.
b. After resting 5 minutes supine and 2 minutes standing.
c. Prior to VPP after resting 5 minutes supine.
d. Prior to VPP and upon completion of VPP.

Table 2. Visit Schedule Part B

	Screen	Familiarization (Occurred at Screen)	Period 1	Period 2	Period 3	Period 4	Follow-up
Written informed consent	X						
Demographics	X						
Medical history	X						
Serum pregnancy test	X						
Laboratory safety	X		X[a]	X[a]	X[a]	X[a]	X
Blood test testosterone/estradiol	X						
ECG	X						
Gynecological examination	X						
Physical examination	X		X[b]	X[b]	X[b]	X[b]	X
Blood pressure/pulse rate	X[c]		X[d]	X[d]	X[d]	X[d]	X
Drugs of abuse	X		X[a]	X[a]	X[a]	X[a]	
Breath alcohol			X[a]	X[a]	X[a]	X[a]	
Sexual function questionnaire/ distress question	X						
Semi-structured interview	X						
Urine pregnancy test			X[a]	X[a]	X[a]	X[a]	X
Soluble biomarkers, such as ANP, big endothelin.			X[e]	X[e]	X[e]	X[e]	
Dosing			X	X	X	X	
Arousal questionnaire			X[b]	X[b]	X[b]	X[b]	
VPP with VSS		X (5 mins session)	X	X	X	X	
Pharmacokinetic sample			X[e]	X[e]	X[e]	X[e]	
Concomitant treatment/ non- drug treatment	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

ANP = atrial natriuretic peptide; ECG = electrocardiogram; Screen = screening; VPP = vaginal photoplethysmography; VSS = visual sexual stimulation.

a. Prior to dosing.
b. Prior to VPP and upon completion of VPP.
c. After resting 5 minutes supine and 2 minutes standing.
d. Prior to VPP and upon completion of VPP after resting 5 minutes supine.
e. Prior to VPP and upon completion of VPP (1 h 05 mins postdose).

Number of Subjects (Planned and Analyzed): A total of 36 subjects were planned for the analysis, of which 38 subjects who were screened, 34 subjects: 16 subjects were enrolled in Part A and 18 subjects were randomized and dosed in Part B.

Diagnosis and Main Criteria for Inclusion: All subjects (Part A and Part B) were pre-menopausal female subjects, Part A aged between 20-48 and Part B 22-48, who had been in a stable heterosexual relationship for at least 3 months prior to study start and remained in a stable relationship throughout the duration of the study were included in the study. Additionally, subjects who were suffering from FSAD must have had this condition present for at least 6 months prior to study entry, which might not had been associated with female orgasmic disorder and/or superficial/introital dyspareunia.

Main Criteria for Exclusion: Subjects who were post-menopausal; subjects who had an oestradiol plasma concentration of <40 pg/mL; oestradiol levels were only required in

subjects who were not taking oestrogen-containing oral contraception; subjects with a recent (past 6 months) history of alcohol or controlled substance abuse; subjects who had given birth in the previous 6 months, were pregnant, lactating or planning to become pregnant during this study; subjects with recent (past 3 months) exacerbation of pelvic inflammatory disease, a recent untreated vaginal infection, salpingitis, or other severe or chronic gynaecologic disease were excluded from the study. Additionally, subjects who were suffering from FSAD were excluded if they also suffered from HSDD; subjects whose sexual dysfunction was considered to be situational; subjects receiving hormonal replacement treatment or subjects whose sexual dysfunction could be explained by any other major psychological or sexual disorder.

Study Treatment:

Part A: No treatment was administered during this part of the study.

Part B: During the 4 treatment periods, subjects received 3 doses of UK-447,841 (10, 50 and 400 mg) as well as placebo as oral solutions. During each of the treatment periods, each subject received 100 mL of UK-447,841/placebo solution 15 minutes after commencing VPP while remaining in semi-recumbent or sitting position with the VPP probe in place.

Efficacy, Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Part A:

Primary Endpoints:

- Natural log transformation (ln) VPA mean change from ln baseline to mean VSS as measured by VPP;
- Ln VPA mean change from ln baseline to maximum level during VSS as measured by VPP.

Secondary Endpoints:

- Visual inspection of VPP traces;
- Subjective feeling of arousal as measured by subjective self-assessment of arousal questionnaire.

Part B:

Primary Endpoints:

- Ln VPA mean change from pre-dose ln baseline to mean VSS as measured by VPP;
- Ln VPA mean change from pre-dose ln baseline to maximum level during VSS as measured by VPP.

Secondary Endpoints:

- Ln VPA mean change from pre-dose ln baseline to the pre-VSS neutral video phase as measured by VPP.

- Subjective feeling of arousal during VSS as measured by subjective self-assessment of arousal questionnaire.

- Safety and toleration of UK-447,841 as measured by: Adverse event (AE) reporting, laboratory safety testing, physical examination, supine BP and PR measurements.

- Plasma concentration of UK-447,841 pre-dose and post-VPP (1 hour 05 mins postdose).

- Levels of plasma biomarkers (such as VIP, ANP, cGMP and big endothelin) pre-dose and post-VPP (1 hour 5 mins postdose).

Safety Evaluations: AEs were recorded from screening until Study Period 3 (Part A) or the follow-up assessment, 7 to 14 days after subject's last dose (Part B). Blood samples for haematology and serum biochemistry, and urine sample for urinalysis tests were collected at screening for subjects in Parts A and B. Additional samples were collected for subjects in Part B upon admission to the clinic during each study period and at the follow-up visit. Subjects had a full physical examination at screening, on admission to the clinic before each study period and, in Part B, before discharge from the clinic at the end of each study/treatment period and at the follow-up visit. Supine and standing BP and PR measurements were recorded at screening using a semi-automated sphygmomanometer after resting supine for 5 minutes and standing for 2 minutes. During each study period, supine BP and PR measurements were recorded prior to VPP and upon completion of VPP after resting for 5 minutes supine. For subjects in Part B, supine BP and PR measurements were taken at the follow-up visit as well. A 12-lead electrocardiogram (ECG) was recorded after resting for 5 minutes supine at screening for both Parts A and B of the study.

Statistical Methods:

The following population sets were analyzed:

Per Protocol Analysis Sets:

Efficacy Analysis Set: Subjects having VPA data on placebo and at least 1 active dose were included for efficacy analysis in Part B.

Pharmacodynamic (PD) Analysis Set: It included subjects who did not violate any major inclusion/exclusion criteria, and received UK-447,841 or placebo and provided at least 1 PD measurement.

Pharmacokinetic (PK) Analysis Set: It included subjects who did not violated any major inclusion/exclusion criteria, and received UK-447,841 and provided at least 1 PK concentration.

Safety Analysis Set: It included subjects who received at least 1 dose of UK-447,841 or placebo.

The primary endpoints were listed and summarized by period. The same primary endpoints pooled across all sites were subjected to an exploratory analysis of variance to assess between and within subject variability for Part A, and an analysis of covariance was used for Part B. For Part B, differences between treatment means, standard errors of these differences and 95% confidence intervals (CIs) for the differences were presented. The differences and CIs were back transformed to give an estimate that was a ratio of the effect of UK-447,841 relative to placebo.

The plasma concentrations of UK-447,841 were plotted and plasma concentration response relationships were investigated as appropriate and summarized by treatment and time postdose. For each of ANP and big-endothelin biomarkers, mean plots versus time postdose (where the time-points are 'predose' and 1 hour 5 minutes postdose) were produced by treatment. This data was also listed and summarized by treatment and time postdose. The safety endpoints were listed and summarized in accordance with the sponsor's worldwide safety standards Version 3.

RESULTS

Subject Disposition and Demography: Of the 38 subjects who were screened, 34 subjects (16 subjects in Part A assigned to non-drug treatment and 18 subjects in Part B were assigned to study treatment) were assigned to study treatment and 31 subjects (16 subjects in Part A and 15 subjects in Part B) completed the study. Three subjects were screened but did not participate in the study as they did not meet entrance criteria, while 1 subject decided not to participate in the study after screening. No discontinuations were reported during Part A of the study. However, in Part B, there were 3 discontinuations. None of the discontinuations were considered to be treatment-related. Two subjects were discontinued from the study as they were lost to follow-up while 1 subject discontinued from the study, as she was no longer willing to participate in the study. Table 3 summarizes the subject disposition.

Table 3. Subject Disposition

Number of Subjects	Part A		UK-447,841			Double-Blind Placebo
	Healthy Subjects	FSAD Subjects	10 mg	50 mg	400 mg	
Screened 38						
Treated	8	8	17	17	18	17
Completed	8	8	16	17	16	17
Discontinued	0	0	1	0	2	0
Analyzed for PK	0	0	17	17	18	17
Analyzed for PD	0	0	17	17	18	17
Analyzed for safety						
AEs	8	8	17	17	18	17
Laboratory data	0	0	7	9	6	13
Vital signs	8	8	17	17	18	17
ECG	8	8	17	17	18	17

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
No study treatment was given to subjects in Part A.
Subjects in Part A were not analyzed for PK or PD.
Laboratory records were taken predose only in each treatment period, therefore records were allocated to screening for Period 1 or to previous treatments for other periods.
AEs = adverse events; ECG = electrocardiogram; FSAD = female sexual arousal disorder; PK = pharmacokinetic; PD = pharmacodynamics.

All subjects were white females. Table 4 below summarizes the demography and baseline characteristics.

Table 4. Demography and Baseline Characteristics

Number of Subjects	Part A (N=16)	Part B (N=18)
Age (Years)		
Mean (SD)	30.5 (7.7)	32.4 (6.5)
Range	20-48	22-48
Weight (Kg)		
Mean (SD)	67.2 (11.5)	65.7 (9.1)
Range	49.1-97.2	47.6-80.6
Height (cm)		
Mean (SD)	167.6 (6.8)	166.0 (8.8)
Range	152.0-178.0	148.0-185.0

N = number of subjects; SD = standard deviation.

Efficacy, Pharmacokinetic, Pharmacodynamic Results:

Primary Endpoints:

Ln VPA Mean Change From Baseline and ln VPA Maximum Change From Baseline During VSS:

Part A: Mean and maximum change from baseline in VPA during VSS were similar in each treatment period for healthy subjects (range: 0.70 to 0.78 for mean VPA and 0.92 to 0.99 for maximum VPA) indicating that the VPP technique provided reproducible results. The results were lower and more variable in subjects with FSAD (range: 0.51 to 0.77 for mean VPA and 0.66 to 0.95 for maximum VPA, Table 5).

Part B: Watching erotic videos resulted in an increase in VPA in all groups. Mean and maximum changes from baseline VPA were similar in each treatment group including placebo (Table 5). UK-447,841 had no statistically significant effect on these parameters compared to placebo. The largest numerical effect was observed in the 50 mg dose group. However, the ratio of this group relative to placebo in the log VPA mean change from baseline during VSS was 1.09 (95% CI=0.92, 1.3). A ratio of 1 indicated no difference to placebo (Table 6). There were no statistical significant differences between any dose of UK-447,841 and placebo in ln VPA maximum change from baseline during VSS. The ratio of 50 mg dose group relative to placebo in the ln VPA maximum change from baseline during VSS was 1.08 (95% CI=0.90, 1.3). The magnitude of corresponding treatment difference was very similar for the neutral phase (Table 7). Between subjects variability was large.

Table 5. Summary of Ln VPA Change (Mean and Maximum) From Ln Baseline During VSS for Part A and Part B

Parameter	Part A						Part B			
	Healthy Subjects			FSAD Subjects			UK-447,841			Double-Blind Placebo
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	10 mg	50 mg	400 mg	
VPA (mean)	0.72	0.78	0.70	0.51	0.77	0.56	0.74	0.80	0.77	0.71
SD (mean)	0.33	0.49	0.45	0.37	0.38	0.30	0.41	0.46	0.38	0.32
CV (%)	46.3	63.4	63.6	72.8	48.7	53.4	55.6	57.6	49.7	45.3
VPA (max)	0.93	0.99	0.92	0.66	0.95	0.78	0.94	0.98	0.93	0.91
SD (max)	0.30	0.49	0.44	0.35	0.40	0.31	0.41	0.47	0.39	0.30
CV (%)	32.1	49.7	47.4	52.8	42.3	40.1	43.7	47.6	42.0	33.3

CV=coefficient of variance; FSAD=female sexual arousal disorder; Ln = natural log transformation; SD=standard deviation; VSS=visual sexual stimulation; VPA=vaginal pulse amplitude.

Table 6. Summary of Statistical Analysis of Ln VPA Mean Change From Baseline During VSS

Dose	Log Transformed Difference Between Means	Log Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg / double-blind placebo	0.04	0.087	1.04	(0.88, 1.24)	0.631
UK-447,841 50 mg / double-blind placebo	0.09	0.086	1.09	(0.92, 1.30)	0.312
UK-447,841 400 mg / double-blind placebo	0.07	0.086	1.07	(0.90, 1.27)	0.433

The ratio and corresponding confidence limits are back transformed from the natural log scale.
CI = confidence interval; Ln = natural log transformation; VPA = vaginal pulse amplitude; VSS = visual sexual stimulation.

Table 7. Summary of Statistical Analysis of Ln VPA Maximum Change From Baseline During VSS

Dose	Log Transformed Difference Between Means	Log Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg / double-blind placebo	0.05	0.093	1.05	(0.87, 1.27)	0.597
UK-447,841 50 mg / double-blind placebo	0.07	0.091	1.08	(0.90, 1.29)	0.422
UK-447,841 400 mg / double-blind placebo	0.04	0.091	1.04	(0.86, 1.25)	0.694

The ratio and corresponding confidence limits are back transformed from the natural log scale.
CI = confidence interval; Ln = natural log transformation; VPA = vaginal pulse amplitude; VSS = visual sexual stimulation.

Secondary Endpoints:

Ln Mean Change From Baseline During Neutral Video Phase:

Part A and Part B: During the neutral video phase, there were minimal changes in mean VPA (Table 8). Table 8 below summarizes the ln VPA mean change from baseline during neutral video phase for both the parts.

Table 8. Summary of Ln VPA Mean Change From Baseline During Neutral Video Phase for Part A and Part B

Parameter	Part A						Part B			
	Healthy Subjects			FSAD Subjects			UK447,841			Double-Blind Placebo
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	10 mg	50 mg	400 mg	
VPA (mean)	-0.02	0.04	-0.003	-0.03	0.11	0.06	0.14	0.18	0.16	0.13
SD (mean)	0.08	0.10	0.22	0.11	0.17	0.12	0.19	0.25	0.15	0.18
CV (%)	-489.8	258.6	-8839.1	-319.7	160.3	208.8	135.2	140.8	90.9	138.8

CV = coefficient of variance; FSAD = female sexual arousal disorder; Ln = natural log transformation; SD = standard deviation; VPA = vaginal pulse amplitude.

Part B: There were no statistical significant differences between any dose of UK-447,841 and placebo in ln VPA mean change from baseline during first neutral video. Table 9 summarizes the statistical analysis of ln VPA mean change from baseline during first neutral period.

Table 9. Summary of Statistical Analysis of Ln VPA Mean Change From Baseline During First Neutral Period

Dose	Log Transformed Difference Between Means	Log Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg / double-blind placebo	0.01	0.068	1.02	(0.89, 1.16)	0.833
UK-447,841 50 mg / double-blind placebo	0.04	0.067	1.04	(0.91, 1.19)	0.582
UK-447,841 400 mg / double-blind placebo	0.03	0.067	1.03	(0.90, 1.18)	0.683

The ratio and corresponding confidence limits are back transformed from the natural log scale.
CI = confidence interval; Ln = natural log transformation; VPA=vaginal pulse amplitude.

Subjective Self-Assessment of Arousal Questionnaire:

Part A: For Part A, there was consistently a higher response in the healthy subjects compared to FSAD subjects following VSS. For healthy subjects, the response scores were higher for Question 1 (sexually aroused) followed by Question 2 (mentally sexually aroused), and Question 4 (genital feelings) in Period 1. While for FSAD subjects, the response score was highest for Question 2 in Period 1. There was no obvious correlation between mean VPA change from baseline and change in subjective self-assessment of arousal at VSS. Summary of mean change from baseline in subjective self-assessment of arousal questionnaire for Part A is summarized in Table 10.

Table 10. Summary of Mean Change From Baseline in Subjective Self-Assessment of Arousal Questionnaire (Part A)-Arithmetic Means

Question	Healthy Subjects			FSAD Subjects		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
Sexually aroused	3.8	2.9	3.1	1.3	1.0	1.0
Mentally sexually aroused	3.5	2.8	2.9	1.4	1.0	0.6
Physically sexually aroused	3.4	2.9	3.0	0.9	1.1	0.8
Genital feelings	3.5	2.6	3.3	1.1	0.8	1.3
Feelings of warmth	3.0	2.5	2.4	0.7	0.8	1.1
Genital pulsing	3.4	2.9	3.3	0.5	0.6	0.9
Warmth of genitals	3.3	2.9	3.0	0.9	1.1	1.3

Subjects were assessed on a 0-7 scale.
FSAD = female sexual arousal disorder.

Part B: There was no clinically meaningful difference between any treatment dose and placebo. There was no obvious correlation between mean VPA change from baseline and change in subjective self-assessment of arousal at VSS. Summary of mean change from baseline in subjective self-assessment of arousal questionnaire for Part B is summarized in Table 11.

Table 11. Summary of Mean Change From Baseline in Subjective Self-Assessment of Arousal Questionnaire (Part B)-Arithmetic Means

Question	UK-447,841			
	10 mg	50 mg	400 mg	Double-Blind Placebo
Sexually aroused	1.6	1.6	1.9	2.0
Mentally sexually aroused	1.5	1.5	1.6	1.7
Physically sexually aroused	1.7	1.7	1.7	1.9
Genital feelings	1.8	1.8	1.7	2.0
Feelings of warmth	1.6	1.5	1.6	1.9
Genital pulsing	1.4	1.6	1.5	1.8
Warmth of genitals	1.7	1.6	1.7	2.1

Subjects were assessed on a 0-7 scale.

Pharmacokinetics (Part B): The mean plasma concentrations of UK-447,841 at 1 hour 5 minutes postdose were 0.5, 5.2, and 22.6 ng/mL for the 10, 50, and 400 mg treatment groups, respectively showing an increase with dose (Table 12). There was no obvious correlation between mean and maximum VPA change from baseline during VSS and neutral video phase versus UK-447,841 plasma concentration at 1 hour 5 minutes postdose.

Table 12. Summary of UK-447,841 Pharmacokinetic Concentrations - Part B

Nominal Time Postdose	Mean (ng/ml)	SD (ng/ml)	%CV	N[a]	NALQ[b]
Treatment Group: UK-447,841 10 mg					
0 h	-	-	-	17	1
1 h 5 min	0.5	0.26	54.1	16	14
Treatment Group: UK-447,841 50 mg					
0 h	-	-	-	17	0
1 h 5 min	5.2	7.35	140.9	15	15
Treatment Group: UK-447,841 400 mg					
0 h	-	-	-	18	0
1 h 5 min	22.6	12.11	53.6	15	15

The lower limit of quantification is 0.001 ng/ml.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to 0.
The mean, SD and CV were not calculated if >50% of data at a specific nominal time postdose were missing.
CV = coefficient of variance; N = number of non-missing concentration values; NALO = Number of concentration values above the lower limit of quantification; SD = standard deviation.
a. Number of non-missing concentration values.
b. Number of concentration values above the lower limit of quantification.

Pharmacodynamics (Part B): There was an increase in ANP levels at 1 hour 5 minutes postdose compared to predose (0 hour) following treatment with UK-447,841 400 mg and UK-447,841 50 mg. However, there was a decrease in the ANP level at 1 hour 5 minutes postdose compared to predose following treatment with UK-447,841 10 mg and placebo.

There appeared to be a dose related increase in the big endothelin levels at 1 hour 5 minutes postdose compared to predose (0 hour) following treatment with each dose of UK-447,841. The increase in the big endothelin levels was highest following treatment with UK-447,841 400 mg and appeared to be dose related. There was a decrease in big endothelin levels at 1 hour 5 minutes postdose compared to predose (0 hour) following treatment with placebo. Table 13 presents the summary of PD data for ANP and big endothelin-1.

Table 13. Summary of Pharmacodynamic Data

Pharmacodynamic Parameter	Time Postdose	UK-447,841			
		10 mg	50 mg	400 mg	Double-Blind Placebo
ANP	0 hour				
	Mean (SD)	57.7 (16.29)	58.9 (13.88)	56.9 (11.91)	58.4 (14.86)
	Range	33-88	40-87	35-73	38-95
	1 hour 5 minutes				
	Mean (SD)	56.1 (11.70)	64.2 (9.19)	83.0 (14.35)	56.1 (9.31)
	Range	33-83	49-83	55-106	34-69
Big Endothelin-1	0 hour				
	Mean (SD)	9.6 (29.10)	9.0 (27.11)	9.8 (30.05)	10.9 (35.62)
	Range	0-122	0-114	0-126	0-149
	1 hour 5 minutes				
	Mean (SD)	9.9 (25.19)	11.9 (29.97)	13.7 (32.64)	9.5 (26.97)
	Range	0-107	2-128	3-140	0-114

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.
ANP = atrial natriuretic peptide; SD=standard deviation.

Safety Results:

Overview of Safety Results:

Part A: Of the 8 healthy subjects evaluated for AEs, 1 subject reported a treatment emergent AEs (TEAEs). Of the 8 FSAD subjects evaluated for AEs, 1 subject reported 2 TEAEs.

Part B: During the treatment phases, 5, 5, 3 and 12 TEAEs were reported for the UK-447,841 10 mg, 50 mg, 400 mg and placebo treatment phases, respectively. All AEs were either mild or moderate in severity. Table 14 below summarizes treatment emergent AEs (All Causalities).

Table 14. Summary of Adverse Events

	Part A		Part B			
			UK-447,841			Double-Blind Placebo
	Healthy Subjects	FSAD Subjects	10 mg	50 mg	400 mg	
Subjects Evaluable for AE						
All Causality	8 (8)	8 (8)	17 (17)	17 (17)	18 (18)	17 (17)
Number of AEs						
All Causality	1 (1)	2 (2)	5 (5)	5 (2)	3 (3)	12 (5)
Subjects with AEs						
All Causality	1 (1)	1 (1)	3 (3)	4 (1)	2 (2)	6 (4)

Values in parenthesis indicate treatment-related.
AE = adverse event; FSAD = female sexual arousal disorder.

Incidence of TEAEs (all-causality) and treatment-related are presented in Table 15 and Table 16, respectively.

Table 15. Incidence of Treatment-Emergent Adverse Events (All Causalities)

System Organ Class and MedDRA (v8.1) Preferred Term	Part A		Part B			
			UK-447,841			Double-Blind Placebo (N=17)
	Healthy Subjects (N=8)	FSAD Subjects (N=8)	10 mg (N=17)	50 mg (N=17)	400 mg (N=18)	
	n	n	n	n	n	n
Cardiac disorders	0	0	1	0	0	0
Palpitations	0	0	1	0	0	0
Ear and labyrinth disorders	0	0	0	1	0	0
Ear pain	0	0	0	1	0	0
Gastrointestinal disorders	0	0	2	1	0	4
Abdominal discomfort	0	0	1	0	0	1
Abdominal pain lower	0	0	0	0	0	1
Diarrhoea	0	0	0	1	0	1
Nausea	0	0	1	0	0	2
Injury, poisoning and procedural complications	0	1	0	0	0	0
Post procedural complication	0	1	0	0	0	0
Musculoskeletal and connective tissue disorders	1	0	0	0	0	1
Myalgia	1	0	0	0	0	0
Neck pain	0	0	0	0	0	1
Nervous system disorders	0	0	1	1	0	3
Dizziness	0	0	1	0	0	1
Headache	0	0	0	0	0	2
Hypoaesthesia	0	0	0	0	0	1
Paraesthesia	0	0	0	0	0	1
Syncope vasovagal	0	0	0	1	0	0
Renal and urinary disorders	0	0	0	1	1	1
Micturition urgency	0	0	0	1	1	1
Reproductive system and breast disorders	0	1	0	1	0	0
Breast engorgement	0	0	0	1	0	0
Vaginal discharge	0	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1	0
Nasal discomfort	0	0	0	0	1	0
Skin and subcutaneous tissue disorders	0	0	1	0	1	0
Pruritus	0	0	0	0	1	0
Rash erythematous	0	0	1	0	0	0

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v8.1) coding dictionary applied.
FSAD = female sexual arousal disorder; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = Number of Subjects evaluable for adverse events; v = version.

Table 16. Incidence of Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class and MedDRA (v8.1) Preferred Term	Part A		Part B			
			UK-447,841			Double-Blind Placebo (N=17)
	Healthy Subjects (N=8)	FSAD Subjects (N=8)	10 mg (N=17)	50 mg (N=17)	400 mg (N=18)	
	n	n	n	n	n	n
Cardiac disorders	0	0	1	0	0	0
Palpitations	0	0	1	0	0	0
Gastrointestinal disorders	0	0	2	0	0	2
Abdominal discomfort	0	0	1	0	0	1
Nausea	0	0	1	0	0	1
Injury, poisoning and procedural complications	0	1	0	0	0	0
Post procedural complication	0	1	0	0	0	0
Musculoskeletal and connective tissue disorders	1	0	0	0	0	0
Myalgia	1	0	0	0	0	0
Nervous system disorders	0	0	1	0	0	1
Dizziness	0	0	1	0	0	0
Hypoaesthesia	0	0	0	0	0	1
Paraesthesia	0	0	0	0	0	1
Renal and urinary disorders	0	0	0	1	1	1
Micturition urgency	0	0	0	1	1	1
Reproductive system and breast disorders	0	1	0	1	0	0
Breast engorgement	0	0	0	1	0	0
Vaginal discharge	0	1	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1	0
Nasal discomfort	0	0	0	0	1	0
Skin and subcutaneous tissue disorders	0	0	1	0	1	0
Pruritus	0	0	0	0	1	0
Rash erythematous	0	0	1	0	0	0

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v8.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = Number of Subjects evaluable for adverse events; v = version.

Serious Adverse Events (SAEs): One subject reported an SAE of recurrent tonsillitis while receiving UK-447,841 400 mg. The subject recovered after hospitalisation. However, the SAE was not considered related to study drug due to the subject's history of recurrent tonsillitis.

Deaths: There were no deaths reported during the study.

Discontinuations Due to AEs: There were no permanent and temporary discontinuations or dose reductions due to AEs.

Laboratory Evaluations: None of the laboratory abnormalities, vital signs and ECG data were considered to be clinically significant.

CONCLUSIONS: The VPP technique produces reproducible results in healthy subjects and subjects with FSAD. There was greater variability in subjects with FSAD but this was within acceptable limits.

There was a clear increase in VBF following VSS compared to neutral phases.

There were no statistically significant differences between any dose of UK-447,841 and placebo in VBF as measured by VPP during the erotic and neutral phases, for this group of pre-menopausal subjects suffering from FSAD. Also, the plasma biomarker data (big endothelin and ANP) confirmed that pharmacological active doses were tested. This suggests that the lack of effect seen was due to lack of drug effect.

All reported AEs were mild or moderate in severity. None of the AEs were severe. There were no deaths or discontinuations reported during the study. One subject reported a SAE of recurrent tonsillitis, which was not considered, related to study treatment. None of the laboratory abnormalities were considered to be clinically significant. There were no clinically significant changes in vital signs and ECG.