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COMPOUND NUMBER: UK-447,841

PROTOCOL NO.: A5031004

PROTOCOL TITLE: A Two Part Study to A) Investigate the Reproducibility of the Vaginal Photoplethysmography (VPP) Technique in Healthy Post-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 (VBF) in Post-Menopausal Subjects Suffering from FSAD

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

Study Initiation and Final Completion Dates: 05 February 2005 to 01 March 2006

Phase of Development: Phase 2A

Study Objectives:

Part A:

- Primary:
  - To investigate the reproducibility of the vaginal photoplethysmography (VPP) technique in healthy post-menopausal female volunteers and post-menopausal subjects suffering from female sexual arousal disorder (FSAD).
- Secondary:
  - To assess the degree of undesirable artefacts and fluctuations in the vaginal pulse amplitude (VPA) traces.
  - To assess the variability of 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:
  - To investigate the effect of single doses of UK-447,841 on vaginal blood flow (VBF) as measured by VPP in post-menopausal subjects suffering from FSAD.
- Secondary:
  - 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 to a) investigate the reproducibility of the VPP technique in 8 healthy post-menopausal volunteers and 8 post-menopausal subjects suffering from FSAD and b) 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 to 24 post-menopausal subjects suffering from FSAD based upon the variability observed in Part A.

Part A: This part consisted of a screening/familiarization visit followed by 3 study periods. Each study period was separated by at least 2 days (48 hours). Each study period lasted for approximately 2 hours in the clinic. There was no follow-up visit. No study drug was administered during this part of the study. A brief arousal questionnaire was administered prior to and post-VPP to determine levels of arousal during baseline and VSS. Part A was completed and data reviewed before progressing to Part B. No site was allowed to progress to Part B until all subjects had completed Part A, data had been reviewed and acceptable reproducibility confirmed. Table 1 summarizes the timetable of study procedures/evaluations for Part A.

Part B: This part consisted of a screening/familiarization visit followed by 4 treatment periods and a follow-up visit. Each treatment period was separated by at least 4 days. Each treatment period lasted for approximately 2 hours in the clinic. A follow-up visit took place 7 to 14 days after the last treatment period. During each treatment period, subjects attended the clinic after fasting for 2 hours prior to dosing. During Study Period B, blood samples

were collected predose and at 1 hour 5 minutes postdose for pharmacokinetic (PK) assessments and for pharmacodynamics (PD) analysis of soluble biomarkers such as ANP and big-endothelin. Table 2 summarizes the timetable of study procedures/evaluations for Part B.

Table 1. Visit Schedule – Part A

	Scr.	Familiarization (May Take Place at Scr.)	Period 1	Period 2	Period 3
Written informed consent	X				
Demographics	X				
Medical history	X				
Laboratory safety	X				
Blood test testosterone/estradiol	X				
ECG	X				
Gynecological examination	X				
Physical examination	X		X[a]	X[a]	X[a]
BP/PR	X[b]		X[c]	X[c]	X[c]
Urine drugs of abuse	X		X[a]	X[a]	X[a]
Alcohol breath test			X[a]	X[a]	X[a]
Sexual function questionnaire/ distress question	X				
Arousal questionnaire			X[d]	X[d]	X[d]
VPP with VSS		X (5 min session)	X	X	X
Concomitant treatment/non-drug treatment	X	X	X	X	X
AEs	X	X	X	X	X

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; PR = pulse rate; Scr. = 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

	Scr.	Familiarization (May Take Place at Scr.)	Period 1	Period 2	Period 3	Period 4	Follow-Up
Written informed consent	X						
Demographics	X						
Medical history	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
BP/PR	X[c]		X[d]	X[d]	X[d]	X[d]	X
Urine drugs of abuse	X		X[a]	X[a]	X[a]	X[a]	
Alcohol breath test			X[a]	X[a]	X[a]	X[a]	
Sexual function questionnaire/distress question	X						
Soluble biomarkers, such as ANP and 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 min session)	X	X	X	X	
PK sample			X[e]	X[e]	X[e]	X[e]	
Concomitant treatment/ non-drug treatment	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X

AE = adverse event; ANP = atrial natriuretic peptide; BP = blood pressure; ECG = electrocardiogram; PK = pharmacokinetic; PR = pulse rate; Scr. = 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 hour 05 minutes postdose).

Number of Subjects (Planned and Analyzed): For Part A, a sample size of 8 healthy volunteers and 8 subjects with FSAD was chosen to provide sufficient results. After Part A was completed, based on the variability observed, the sample size for Part B was revised from 16-24 completed subjects to 12 completed subjects. Eight (8) subjects in the UK, 5 subjects in Australia, and 14 subjects in Norway were enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

All Subjects: Post-menopausal female subjects aged 45-65 years, 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.

FSAD Subjects: Subjects who were suffering from FSAD for at least 6 months prior to study entry, which may or may not have been associated with female orgasmic disorder and/or superficial/introital dyspareunia were included in the study.

Exclusion Criteria:

All Subjects: Subjects with a history of involuntary movement disorders, gynecological malignancy or abnormal cervical cytology suggestive of neoplastic changes, exacerbation of pelvic inflammatory disease, untreated vaginal infection, salpingitis, or other severe or chronic gynecologic disease within 3 months prior to the start of study, who had an estradiol plasma concentration of <40 pg/mL, who were taking selected estrogen receptor modulator, such as raloxifen or tamoxifen, or who had previous surgery to the vagina, were excluded from the study.

FSAD Subjects: Subjects who suffered from hypoactive sexual desire disorder and whose sexual dysfunction was considered to be situational, who were taking medication known to interact with neutral endopeptidase-inhibitors such as angiotensin converting enzyme inhibitors, who were participating in a structured psychosexual therapy program at the time of recruitment, who had significant dyspareunia, inadequately controlled diabetes, thyroid dysfunction or clinically significant hyperprolactinemia, were excluded from the study.

Healthy Volunteers: Subjects who had evidence of a female sexual disorder were excluded from the study.

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 a semi-recumbent or sitting position with the VPP probe in place. Sequence of treatment administrations is enlisted in Table 3.

Table 3. Sequence of Treatment Administrations

Sequence	Period 1	Period 2	Period 3	Period 4
I	A	B	C	D
II	C	A	D	B
III	B	D	A	C
IV	D	C	B	A

Where the treatments administered were:
A: Double-blind placebo.
B: UK-447,841 10 mg.
C: UK-447,841 50 mg.
D: UK-447,841 400 mg.

Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Endpoints:

Primary Efficacy Endpoints:

Part A and Part B

- Ln VPA mean change from Ln Baseline as measured by VPP during VSS
- Ln VPA maximum change from Ln Baseline as measured by VPP during VSS

Secondary Efficacy Endpoints:

Part A:

- Visual inspection of VPP traces (study sites were assessed regarding the quality of VPP traces and those with an unacceptable overall level of artifacts in VPA recording were not be allowed to recruit for Part B of the study).
- Subjective feeling of arousal as measured by subjective self-assessment of arousal questionnaire.

Part B:

- Ln VPA mean change from Ln Baseline during neutral video phase as measured by VPP.
- Subjective feeling of arousal as measured by subjective self-assessment of arousal questionnaire.

Safety Evaluations: Safety evaluations including adverse events (AEs) information, laboratory safety tests, electrocardiograms (ECGs), urine drug screen and breath alcohol test, physical examination and vital signs for both parts (Parts A and B) of the study were conducted.

Statistical Methods: All subjects in Part B were included in PK and PD analysis. All subjects in either Part A or Part B were included in the safety analysis (AEs, vital signs, and

ECG). Subjects in Part A were not analyzed for PK and PD as no study drug was administered.

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 results from Part A were used to estimate variability for Part B. The contrasts of interest were:

- UK-447,841 10 mg versus (vs) double-blind placebo.
- UK-447,841 50 mg vs double-blind placebo.
- UK-447,841 400 mg vs double-blind placebo.

For each contrast, UK-447,841 was the 'test' treatment and placebo was the 'reference' treatment.

Individual profiles of VPA vs time were produced for each subject and period. These profiles were visually inspected to assess the degree of undesirable artifacts and fluctuations. These plots were produced at the interim analysis stage at the end of Part A.

For each of the 7 questions in the subjective self-assessment questionnaire of sexual arousal, the subjective feeling of arousal was recorded pre-VPP and post-VPP within each period. For each question, the change (pre/post) was summarized by period.

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.

ANP and big-endothelin biomarkers data were summarized by treatment and time postdose.

The safety endpoints were summarized in accordance with the Sponsor's safety standards.

RESULTS

Subject Disposition and Demography: Of the 31 subjects who were screened, 27 subjects (14 subjects in Part A and 13 subjects in Part B) were assigned to study treatment and all 27 subjects (14 subjects in Part A and 13 subjects in Part B) completed the study. Part A was a non-drug, methodology verification part of the study. Four (4) subjects were screened but did not participate in the study as they did not meet the entrance criteria. No discontinuations were reported during the study. Subject disposition is presented in Table 4.

The 14 subjects in Part A were analyzed for AEs, vital signs, and ECG. They were not analyzed for PK and PD as no study drug was administered. All 13 subjects in Part B were analyzed for PK, PD, AEs, vital signs and ECG.

Part A: All subjects were White females, aged between 46 and 61 years, weighing between 52 and 104 kg, and with a height ranging from 152 to 175 cm. Seven (7) subjects had primary diagnoses of FSAD. The mean duration since first diagnosis (duration in years from first diagnosis to Day 1 of the study) was 7.3 years.

Part B: All subjects were White females, aged between 46 and 64 years, weighing between 54 and 104 kg, and with a height ranging from 158 to 177 cm. Thirteen (13) subjects had primary diagnoses of FSAD. The mean duration since first diagnosis was 5.1 years.

The demographic characteristics are presented in Table 5.

Table 4. Subject Disposition

Number of Subjects	Part A		UK-447,841			Double-Blind Placebo
	Healthy Subjects	FSAD Subjects	10 mg	50 mg	400 mg	
Assigned to study treatment = 27						
Treated	7	7	13	13	13	13
Completed	7	7	13	13	13	13
Discontinued	0	0	0	0	0	0
Analyzed for PK	0	0	13	13	13	0
Analyzed for PD	0	0	13	13	13	13
Analyzed for Safety						
AEs	7	7	13	13	13	13
Laboratory data	0	0	2	6	7	6
Vital signs	7	7	13	13	13	13
ECG	7	7	13	13	13	13

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;
PD = pharmacodynamics; PK = pharmacokinetic.

Table 5. Demographic Characteristics

Number of Subjects	Part A (N=14)	Part B (N=13)
Age (years)		
Mean (SD)	51.5 (5.5)	54.4 (6.7)
Range	46-61	46-64
Weight (kg)		
Mean (SD)	71.2 (13.9)	70.1 (13.6)
Range	52.0-104.0	54.0-104.0
Height (cm)		
Mean (SD)	166.2 (6.6)	165.7 (5.8)
Range	152.0-174.8	158.0-177.0

N = total number of subjects in each part; SD = standard deviation.

Efficacy, Pharmacokinetic and Pharmacodynamic Results:

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

Part A: The results were lower in FSAD subjects (range: 0.72 to 0.86 for mean ln VPA change from Baseline and 0.87 to 1.02 for maximum ln VPA change from Baseline) (Table 6). More variability was seen in Period 3 for the FSAD subjects. The variability observed in Part A of this study was lower than expected and showed that a sample size of 12 subjects was sufficient to detect a relative change of 25% over placebo. Watching erotic videos resulted in an increase in VPA for both healthy and FSAD subjects.

Part B: Based upon the variability observed in Part A, the sample size for Part B was revised from 16-24 completed subjects to 12 completed subjects. Watching erotic videos resulted in a marked increase in VPA in all groups. Mean and maximum changes from Baseline VPA were similar in all treatment groups including placebo (Table 6). UK-447,841 had no statistically significant effect on these parameters compared to placebo. The largest numerical effect was observed in the 400 mg dose group. However, the ratio of this group relative to placebo in the log VPA mean change from Baseline during VSS was 1.14 (95% CI=0.88, 1.48). A ratio of 1 indicated no difference to placebo. The ratio of 400 mg dose group relative to placebo in the ln VPA maximum change from Baseline during VSS was 1.12 (95% CI=0.85, 1.48). There was only a small increase in VPA during VSS compared to neutral/non-erotic video phase. Table 7 summarizes the statistical analysis of ln VPA mean change from Baseline during VSS. Table 8 summarizes the statistical analysis of ln VPA maximum change from Baseline during VSS.

Table 6. 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)	1.28	1.00	0.93	0.86	0.84	0.72	0.77	0.67	0.80	0.67
SD (mean)	0.30	0.26	0.29	0.20	0.19	0.52	0.53	0.45	0.32	0.30
CV (%)	23.7	26.0	30.6	23.5	23.2	71.5	67.8	66.6	40.5	44.7
VPA (max)	1.47	1.23	1.11	1.02	1.01	0.87	0.93	0.84	0.94	0.82
SD (max)	0.29	0.27	0.25	0.20	0.17	0.53	0.55	0.44	0.36	0.32
CV (%)	19.9	21.9	22.4	19.9	16.7	60.3	59.4	52.5	38.8	38.7

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

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

Dose	Ln Transformed Difference Between Means	Ln Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg/ double-blind placebo	0.10	0.128	1.11	(0.85, 1.44)	0.438
UK-447,841 50 mg/ double-blind placebo	0.02	0.128	1.02	(0.78, 1.32)	0.891
UK-447,841 400 mg/ double-blind placebo	0.13	0.129	1.14	(0.88, 1.48)	0.321

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

Table 8. Summary of Statistical Analysis of Ln VPA Maximum Change From Baseline During VSS

Dose	Ln Transformed Difference Between Means	Ln Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg/ double-blind placebo	0.09	0.135	1.10	(0.84, 1.45)	0.492
UK-447,841 50 mg/ double-blind placebo	0.03	0.134	1.03	(0.79, 1.36)	0.808
UK-447,841 400 mg/ double-blind placebo	0.11	0.135	1.12	(0.85, 1.48)	0.403

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

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 9 summarizes the ln VPA mean change from Baseline during neutral video phase for both the parts.

Table 9. 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			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)	0.11	0.05	-0.04	-0.04	0.08	0.02	0.17	0.06	0.06	0.11
SD (mean)	0.23	0.26	0.11	0.15	0.12	0.10	0.36	0.15	0.23	0.13
CV (%)	210.1	565.3	-303.6	-351.0	158.5	458.3	207.1	249.0	361.0	115.6

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

Part B: There were no statistically significant differences between any dose of UK-447,841 and placebo in ln VPA mean change from Baseline during first neutral video. Table 10 summarizes the statistical analysis of ln VPA mean change from Baseline during first neutral period.

Table 10. Summary of Statistical Analysis of Ln VPA Mean Change From Baseline During First Neutral Period

Dose	Ln Transformed Difference Between Means	Ln Transformed Standard Error of Difference	Ratio of Means (%)	95% CI of Ratio (Lower, Upper)	p-Value
UK-447,841 10 mg/ double-blind placebo	0.03	0.092	1.03	(0.85, 1.24)	0.749
UK-447,841 50 mg/ double-blind placebo	-0.06	0.092	0.94	(0.78, 1.14)	0.529
UK-447,841 400 mg/ double-blind placebo	-0.07	0.092	0.93	(0.77, 1.12)	0.428

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

There were no statistically significant differences between any dose of UK-447,841 and placebo on VBF as measured by VPP during the VSS and neutral phases, for this group of post-menopausal subjects suffering from FSAD. The data showed clear increase in VBF following VSS for all treatment groups. The data appeared to be consistent across subjects and treatment groups.

Subjective Self-Assessment of Arousal Questionnaire:

Part A: There was consistently a higher subjective response in the healthy subjects compared to FSAD subjects following VSS. For healthy subjects, the response scores were higher for

Question 2 (mentally sexually aroused) followed by Question 1 (sexually aroused), Question 3 (physically sexually aroused), and Question 7 (warmth of genitals) in Period 1. While for FSAD subjects, the response scores were highest for Questions 2, 5 (feelings of warmth), and 7 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 11.

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

Question	Healthy Subjects			FSAD Subjects		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
	AM	AM	AM	AM	AM	AM
Sexually aroused	3.9	2.6	3.4	1.3	2.1	1.9
Mentally sexually aroused	4.0	2.9	3.4	1.4	2.4	2.0
Physically sexually aroused	3.9	2.7	3.7	1.3	1.6	2.0
Genital feelings	3.7	2.7	3.6	1.3	1.4	1.9
Feelings of warmth	3.7	2.4	3.4	1.4	1.1	1.9
Genital pulsing	3.7	2.7	3.7	1.0	1.4	1.6
Warmth of genitals	3.9	2.3	3.4	1.4	1.3	1.7

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

Part B: There was no clinically meaningful difference between any treatment dose and placebo. A random scatter of VPA data relative to self-assessment questionnaire responses was observed. 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 12.

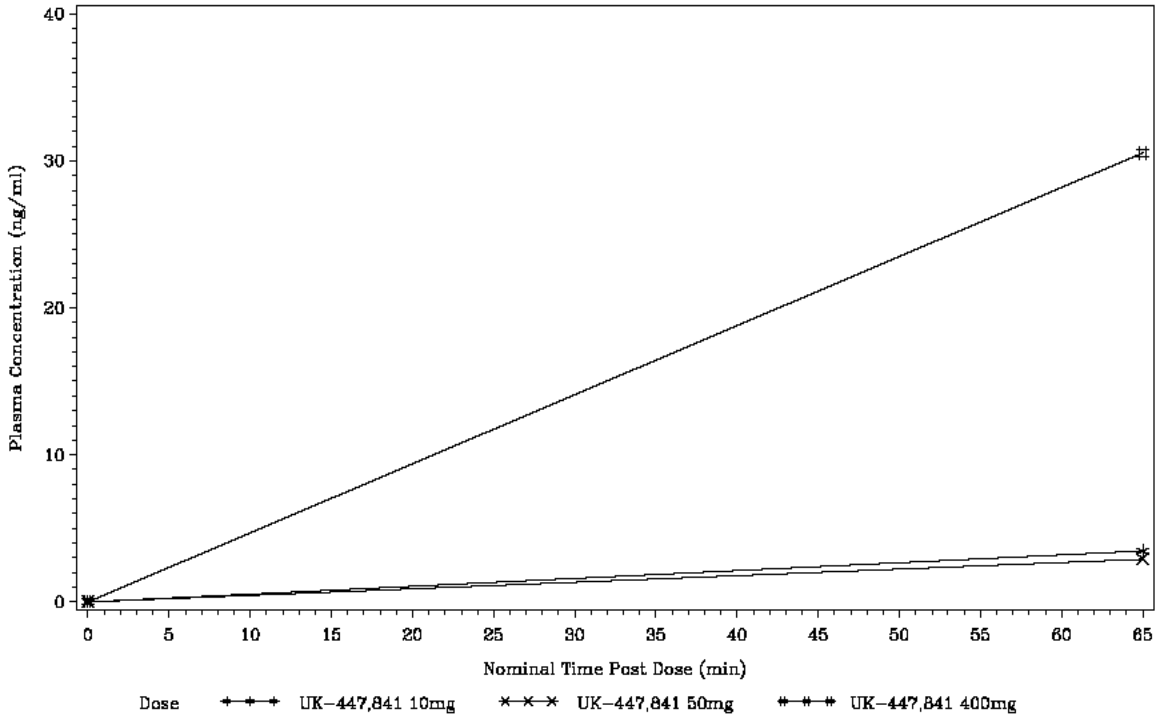
Table 12. Summary of Mean Change From Baseline in Subjective Self-Assessment of Arousal Questionnaire (Part B) - Arithmetic Means

Question	UK-447,841			
	10 mg	50 mg	400 mg	Double-Blind Placebo
Sexually aroused	1.0	2.3	1.9	1.5
Mentally sexually aroused	1.6	2.2	2.0	1.8
Physically sexually aroused	1.2	1.9	1.8	1.6
Genital feelings	1.5	2.5	1.8	2.1
Feelings of warmth	1.1	2.0	1.5	1.6
Genital pulsing	1.4	2.1	1.9	1.7
Warmth of genitals	1.3	2.1	1.6	1.7

Subjects were assessed on a 0-7 scale.

Pharmacokinetic Results (Part B): Plasma concentrations of UK-447,841 were as expected for all dose levels. Figure 1 presents PK concentrations vs dose.

Figure 1. Pharmacokinetic Concentrations Versus Dose



The lower limit of quantification was 0.00100 ng/mL.
Means were calculated by setting concentration values below the lower limit of quantification to 0.
A mean was not calculated if more than 50% of data at a specific nominal time postdose were missing.

Pharmacodynamic Results (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. 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, 50 mg and placebo.

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

Within the limited number of data points, there was no obvious correlation between ANP or big-endothelin-1 vs UK-447,841 plasma concentrations at 1 hour 5 minutes postdose. There was no obvious correlation between mean and maximum VPA change from Baseline during VSS and neutral video phase vs ANP or big-endothelin-1.

Table 13. Summary of Pharmacodynamic Data

Pharmacodynamic Parameter	Time Postdose	UK-447,841 10 mg	UK-447,841 50 mg	UK-447,841 400 mg	Double-Blind Placebo
ANP	0 Hour				
	Mean (SD)	82.9 (25.31)	91.8 (34.43)	86.3 (37.34)	86.1 (27.64)
	Range	48-136	49-184	49-168	47-145
	1 Hour 5 minutes				
	Mean (SD)	77.6 (15.35)	86.8 (25.39)	113.8 (25.97)	73.0 (12.86)
	Range	54-101	50-149	85-186	54-95
Big-endothelin	0 Hour				
	Mean (SD)	1.2 (1.15)	1.4 (1.23)	1.2 (1.06)	1.1 (1.30)
	Range	0-3	0-3	0-3	0-3
	1 Hour 5 minutes				
	Mean (SD)	2.6 (0.91)	3.8 (1.17)	5.2 (1.40)	0.9 (1.29)
	Range	0-3	2-6	2-7	0-3

ANP = atrial natriuretic peptide; SD = standard deviation.

Safety Results:

In Part A, Table 14 and Table 15 summarize treatment-emergent AEs (all causalities) and treatment-emergent AEs (TEAEs) (treatment-related), respectively. One (1) subject had a urinary tract infection on Day 8 and 1 subject had cystitis on Day 3. Both these events were mild in severity and resolved. These AEs are reported on the tables as treatment-related. As no study drug was administered during Part A of the study, these were considered to be device-related.

In Part B, the number of subjects reporting AEs and the number of AEs reported was low. Between 2 and 4 subjects reported AEs during each treatment period. No severe AEs were reported. During the treatment phases, 2, 3, 4 and 2 TEAEs were reported for the UK-447,841 10 mg, 50 mg, 400 mg and placebo treatment phases, respectively.

Table 14. Incidence of Treatment-Emergent Adverse Events (All Causalities)

No. of Subjects Evaluable for AEs	Part A		Part B			
	Healthy Subjects	FSAD Subjects	UK-447,841			Double-Blind Placebo
System Organ Class and MedDRA (v9.0) Preferred Term	n=7	n=7	10 mg n=13	50 mg n=13	400 mg n=13	n=13
Gastrointestinal disorders	0	0	2	0	1	1
Abdominal pain	0	0	0	0	0	1
Bowel sounds abnormal	0	0	1	0	1	0
Nausea	0	0	1	0	0	0
Infections and infestations	1	1	0	0	1	0
Cystitis	0	1	0	0	0	0
Tooth abscess	0	0	0	0	1	0
Urinary tract infection	1	0	0	0	0	0
Nervous system disorders	0	0	0	3	1	0
Headache	0	0	0	0	1	0
Migraine	0	0	0	1	0	0
Paraesthesia	0	0	0	1	0	0
Syncope	0	0	0	1	0	0
Renal and urinary disorders	0	0	0	0	0	1
Glycosuria	0	0	0	0	0	1
Reproductive system and breast disorders	0	0	0	0	1	0
Metrorrhagia	0	0	0	0	1	0
Total preferred term events	1	1	2	3	4	2

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v9.0) coding dictionary applied.
AEs = adverse events; FSAD = female sexual arousal disorder; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; No. = number; v = version.

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

No. of Subjects Evaluable for AEs	Part A		Part B			
	Healthy	FSAD	UK-447,841			Double-Blind
System Organ Class and MedDRA (v9.0) Preferred Term	Subjects n=7	Subjects n=7	10 mg n=13	50 mg n=13	400 mg n=13	Placebo n=13
Gastrointestinal disorders	0	0	2	0	1	1
Abdominal pain	0	0	0	0	0	1
Bowel sounds abnormal	0	0	1	0	1	0
Nausea	0	0	1	0	0	0
Infections and infestations	1	1	0	0	0	0
Cystitis	0	1	0	0	0	0
Urinary tract infection	1	0	0	0	0	0
Nervous system disorders	0	0	0	1	1	0
Headache	0	0	0	0	1	0
Paraesthesia	0	0	0	1	0	0
Reproductive system and breast disorders	0	0	0	0	1	0
Metrorrhagia	0	0	0	0	1	0
Total preferred term events	1	1	2	1	3	1

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v9.0) coding dictionary applied.
AEs = adverse events; FSAD = female sexual arousal disorder; MedDRA = Medical Dictionary for RegulatoryActivities; n = number of subjects; No. = number; v = version.

There were no deaths, serious adverse events (SAEs), permanent or temporary discontinuations or dose reductions reported during the study.

Laboratory Test: Blood samples were collected predose in each treatment period – no clinically significant abnormalities were detected. One (1) subject had raised white blood cells (11.9×10^9/L) and absolute total neutrophils (8.4×10^3/mm^3) values on Day 50 (while treated with double-blind placebo), which were considered clinically significant in the opinion of the Investigator. This was possibly due to upper respiratory tract infection.

Physical Examination (Screening): None of the physical examination findings at Screening were considered to have an impact on the study.

Physical Examination (Changes From Screening): One (1) subject had right medial breast thickening in the post treatment phase (after receiving double-blind placebo).
One (1) subject (after receiving UK-447,841, 50 mg) had syncope lasting for 10 seconds. The subject reacted to blood dripping in her arm and had experienced this previously at the age of 16 years. Her blood pressure (BP) 15 minutes later was 102/65 mm of Hg.

None of the vital signs (BP and pulse rate) or ECG observations were considered to be clinically significant.

CONCLUSIONS:

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 post-menopausal subjects suffering from FSAD. The CIs did not include the planned effect size over placebo. Also, the plasma biomarker data (big-endothelin and ANP) confirmed that pharmacologically 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, SAEs, or discontinuations reported during the study. One (1) of the laboratory abnormalities was considered to be clinically significant and was attributed to upper respiratory tract infection. There were no clinically significant changes in vital signs or ECG readings.