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COMPOUND NUMBER: CP-866,087

PROTOCOL NO.: A5051017

PROTOCOL TITLE: A Phase 2a Multi-Centre, Double-Blind, Placebo Controlled Cross-Over Study to Investigate the Efficacy, Safety and Toleration of CP-866,087 (1 mg-10 mg) in Pre-Menopausal Women Diagnosed With Female Sexual Arousal Disorder (FSAD)

Study Centers: A total of 12 centers took part in the study including 4 in Sweden, 3 in Denmark, 2 each in Australia and South Africa and 1 in Norway.

Study Initiation Date and Final Completion Date: 19 July 2007 to 03 October 2008

Phase of Development: Phase 2

Study Objectives:

- To assess the effect of 3 doses (1, 3 and 10 mg) of CP-866,087 versus placebo on female arousal, desire, orgasm and distress in pre-menopausal women on oral contraceptives suffering primarily from female sexual arousal disorder (FSAD),
- To estimate the effect of 1, 3 and 10 mg doses of CP-866,087 versus placebo on Satisfactory Sexual Events (SSEs) in pre-menopausal women on oral contraceptives suffering primarily from FSAD,
- To develop a dose-response relationship for CP-866,087,
- To assess the safety and tolerability of CP-866,087.

METHODS

Study Design: This was a double-blind, placebo-controlled, control-balanced, incomplete block, 3-way crossover study of CP-866,087, a high affinity mu-opioid receptor antagonist, in female subjects with FSAD. Subjects received placebo and 2 of 3 planned doses of CP-866,087 (1, 3 or 10 mg) for a total of 6 weeks in each treatment period. Subjects attended the clinic on 11 occasions: Screening (Visit 1); start of each treatment period (Visits 2, 5, and 8); safety visits (Visits 3, 6, and 9); end of each treatment period (Visits 4, 7, and 10) and follow-up (Visit 11).

Period 1 was preceded by a 4 week single-blind, placebo run-in, during which subjects received placebo once daily and completed a daily diary to record their sexual activity.

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During the double-blind treatment periods, subjects received blister-packed wallets each containing 7 daily doses of 3 tablets per dose. A follow-up visit occurred 2 weeks after completion of treatment Period 3. The study duration per subject was estimated to be 28 weeks.

A schedule of activities is presented in Table 1.

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Table 1. Schedule of Activities

	Screen Visit 1	Period 1 Start Visit 2	Safety Assessment Visit 3	Period 1 End Visit 4	Period 2 Start Visit 5	Safety Assessment Visit 6	Period 2 End Visit 7	Period 3 Start Visit 8	Safety Assessment Visit 9	Period 3 End Visit 10	Follow-Up Visit 11
Study Day (From Baseline)	**-28**	**1**	**14**	**42**	**57**	**70**	**98**	**113**	**126**	**154**	**170**
Informed consent	X										
ASFQ	X	X		X			X			X	
MFSD	X	X		X			X			X	
Demographics and medical history	X										
Brief physical examination	X	X	X	X	X	X	X	X	X	X	X
Blood pressure/pulse rate	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X	X			X			X			X
Gynaecological examination	X										X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety blood sample	X[a]	X	X	X	X	X	X	X	X	X	X
PD blood sample	X	X	X[b]	X	X	X[b]	X	X	X[b]	X	X
Genotyping blood sample		X									
PK[c] blood sample			X[b]	X[d]		X[b]	X[d]		X[b]	X[d]	
MBQ				X			X			X	
Exit interview										X	
Collect/dispense diary	X	X	X	X	X	X	X	X	X	X	
Check diary compliance		X	X	X		X	X		X	X	
Check drug compliance			X	X		X	X		X	X	
Dispense trial medication wallets	X	X			X			X			
Concomitant medication/non-drug treatment	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities

ASFQ = Abbreviated Sexual Function Questionnaire; ECG = electrocardiogram; MBQ = meaningful benefit question; MFSD = measure of female sexual distress; PD = pharmacodynamic; PK = pharmacokinetic.

a. Additional screening blood samples were taken at Visit 1 only.
b. The samples could have been drawn between 1 and 3 hours postdose and the last dosing and sampling times must have been recorded.
c. Samples to be taken for analysis of CP-866,087.
d. The samples could have been drawn any time within this visit but the last dosing and sampling times must have been recorded.

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Number of Subjects (Planned and Analyzed): Subjects were distributed in >1 treatment section due to cross over design. It was planned to enroll at least 50 subjects, so that no less than 36 subjects would complete all 3 study periods. A total of 51 subjects were randomized in the study.

Diagnosis and Main Criteria for Inclusion: Pre-menopausal females between 20 and 45 years of age, who were diagnosed with FSAD by an experienced female sexual distress therapist/clinician, were included in the study. Subjects had to have evidence of cognitive FSAD as determined by the Abbreviated Sexual Function Questionnaire (ASFQ), based on an AFSQ Arousal-Cognitive Domain score of ≤5, have experienced personal distress due to female sexual dysfunction (FSD) as assessed by the measure of female sexual distress (MFSD), be in a committed and positive heterosexual relationship for at least 6 months at the time of enrollment, and be committed to attempt sexual activity at least twice a week, and on a stable use of chosen combined oral contraceptive for a minimum of 6 months prior to enrollment. Subjects with any other significant disease causing FSD including psychiatric disease, or on drugs known to cause FSD and subjects who had given birth in the last 12 months or who were planning to become pregnant during the study were excluded from the study.

Study Treatment:

Placebo Run-In: Each subject received 4 labeled wallets at Visit 1, each wallet contained 7 daily doses of placebo tablets.

Double-Blind Treatment Periods (1 to 3): One (1), 3 or 10 mg CP-866,087 tablets, or placebo tablets were self-administered once a day in the morning with 125 mL water, for 6 weeks in each treatment period.

The CP-866,087 tablets were of different sizes therefore in order to maintain the blind, each daily dose consisted of 1 large and 2 small tablets.

Efficacy Endpoints:

Efficacy Endpoints:

There is no primary endpoint for this study. However, most interest was in the 3 Arousal Domains of the ASFQ (sensation, cognitive and desire).

Efficacy was measured through an FSD diary and a series of questionnaires designed to assess sexual functioning, sexual activity and sexual distress. The key efficacy endpoints were:

- AFSQ arousal-cognitive domain,
- ASFQ arousal-sensation domain,
- ASFQ desire domain,
- ASFQ orgasm domain,

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- SSEs from the FSD diary.

Safety Evaluations: Safety laboratory tests, vital signs (heart rate, blood pressure), 12-lead electrocardiograms and monitoring of adverse events (AEs) were performed at all visits. Urine pregnancy tests were performed at Visits 1, 2, 5, 8, and 11 (screening, start of each treatment period and follow-up).

Statistical Methods:

Three (3) analysis sets were identified for this study.

- Full Analysis Sets (FAS): The FAS was defined as all subjects who took at least 1 dose of study treatment (post randomization) and had both baseline and on-treatment efficacy for at least 1 endpoint.

- Per Protocol Analysis Set (PPAS): The PPAS was defined as all subjects in the FAS who completed the study and provided approximately 85% or more of the required data at each time period as required by the study, and had not deviated from or violated the study in such a way that could have significantly affected the efficacy outcome. The plan was to have a PPAS for Questionnaire data and a PPAS for Diary data. However, due to the complexity involved in defining these sets, which became apparent during blinded review of the data, a single PPAS was defined instead. The subjects in the PPAS were identified prior to unblinding and consisted of subjects who completed the study and had a score of <5 at Baseline on the arousal-cognitive domain of the ASFQ.

- Safety Analysis Set (SAS): The SAS was defined as those subjects who had taken at least 1 dose of study treatment (post randomization).

The primary and secondary analyses were performed on FAS. The analysis of 3 main arousal domains on the ASFQ (sensation, lubrication and cognitive) were repeated for per protocol analysis datasets. The purpose of this study was estimation, therefore, no p-values were presented and no adjustments of confidence interval (CI) were made to allow for multiplicity of efficacy endpoints.

For efficacy endpoints derived from the ASFQ, MFSD and diary (SSEs), least squares means and 2-sided 90% CIs were calculated for the differences from placebo for each CP-866,087 dose using a mixed effect model analysis of variance (ANOVA) for crossover data. In addition to the above mentioned statistical methods, all efficacy endpoints were described descriptively. The summary statistics (arithmetic mean, median, standard deviation, minimum, maximum and number of subjects included) were provided for each treatment at Baseline and following treatment (CP-866,087 1, 3 and 10 mg and placebo).

This study was designed to estimate the mean of the within-subject differences from placebo in the change from Baseline across a range of efficacy endpoints. Secondary to this was the evaluation of the dose response profile of CP-866,087, across the same efficacy endpoints.

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RESULTS

Subject Disposition and Demography: A total of 65 female subjects were screened. Fifty-one (51) subjects were randomized and 47 subjects were treated with at least 1 dose of either CP-866,087 or double-blind placebo (post randomization). Table 2 presents the number of subjects who were treated with each dose of CP-866,087 and double–blind placebo. Due to the crossover design, subjects were counted in more than 1 treatment column. Although all subjects were randomized to a treatment sequence containing double-blind placebo, and took at least 1 dose from that sequence, 7 subjects discontinued from the study prior to receiving double-blind placebo in their treatment sequence. All treated subjects were analyzed for safety.

Table 2. Subject Evaluation Groups

Number of Subjects		CP-866,087			Double Blind
		1 mg	3 mg	10 mg	Placebo
Screened	65				
Assigned to study treatment	51				
Treated		26	28	27	40
Completed		24	24	24	36
Discontinued		2	4	3	4
Related to study drug					
Adverse event		1	0	2	3
Not related to study drug					
Adverse event		0	1	0	0
Other		0	1	1	0
No longer willing to participate		1	2[a]	0	1
Analyzed for efficacy					
Full analysis set		26	28	27	40
Per-protocol set		21	21	22	32
Analyzed for safety					
Adverse events		26	28	27	40
Laboratory data		26	28	26	40
Safety analysis set		26	28	27	40
ECG		26	27	27	40
Vitals		26	27	27	40

ECG = electrocardiogram.
a. This subject was no longer to participate as there was no perceived positive effect on her condition.

Demographic characteristics are summarized in Table 3.

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Table 3. Demographic Characteristics

	All Treated Subjects
Number of subjects	47
Age (years)	
20-30	34
31-45	13
Mean (SD)	28.8 (5.5)
Race	
White	45
Asian	1
Other	1
Weight	
Mean (SD)	67.8 (10.9)
Height	
Mean (SD)	167.1 (5.8)

All subjects were female.
SD = standard deviation.

Efficacy Results:

Key efficacy data based on the PPAS are presented below in Table 4. The minimal clinically important differences (MCID) for the relevant ASFQ domains were 1.0, 2.0, and 3.0 for arousal-cognitive, arousal-sensation and desire domains, respectively. The ANOVA results for the change from Baseline for ASFQ Arousal-Cognitive Domain, ASFQ Arousal-Sensation Domain, ASFQ Desire Domain and Sexual Activity Satisfaction Score for the PPAS population is presented in Table 5, Table 6, Table 7 and Table 8 respectively.

Table 4. Mean (SD) Baseline and Mean (SD) Change From Baseline for Efficacy Variables (PPAS)

	CP-866,087			Placebo
	1 mg N=21	3 mg N=21	10 mg N=22	N=32
Baseline				
ASFQ arousal-cognitive domain[a]	3.4 (1.12)	3.7 (1.02)	3.64 (1.00)	3.6 (1.05)
ASFQ arousal-sensation domain[b]	7.1 (2.02)	8.0 (1.50)	7.7 (2.13)	7.6 (1.93)
ASFQ desire domain[c]	12.9 (2.48)	12.8 (2.77)	13.5 (2.60)	13.06 (2.61)
Sexual activity satisfaction score from diary[d]	3.3 (0.62)	3.5 (0.61)	3.5 (0.52)	3.4 (0.59)
Satisfactory sexual event[e]	46.5 (30.79)	59.9 (32.40)	57.1 (35.40)	54.5 (33.2)
Change from Baseline				
ASFQ arousal-cognitive domain[a]	1.3 (1.35)	0.6 (1.10)	1.05 (1.80)	1.0 (1.37)
ASFQ arousal-sensation domain[b]	1.7 (2.60)	0.4 (2.35)	1.3 (4.11)	0.94 (2.63)
ASFQ desire domain[c]	2.5 (2.92)	1.4 (4.2)	1.8 (4.41)	1.8 (3.34)
Sexual activity satisfaction sore from diary[d]	0.1 (0.31)	-0.0 (0.44)	-0.1 (0.42)	-0.0 (0.40)
Satisfactory sexual event[e]	51.1 (27.13)	54.8 (26.32)	47.5 (26.59)	51.1 (26.64)

ASFQ = Abbreviated Sexual Function Questionnaire, N = number of subjects per treatment group, PPAS = per protocol analysis set, SD = standard deviation.
a. Score range: 2-10, where 2 indicates the worst response and 10 indicates the best response.
b. Score range: 4-20, where 4 indicates the worst response and 20 indicates the best response.
c. Score range: 5-31, where 5 indicates the worst response and 31 indicates the best response.
d. Score range for change from Baseline: -4 (worst) to +4 (best).
e. Percentage of times the event occurred per subject.

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Table 5. ANOVA Results for Change From Baseline for ASFQ Arousal-Cognitive Domain (PPAS)

Treatment	Number of Subjects	Least Squares Mean Estimate	Difference From Placebo		
			Least Squares Mean Estimate	Standard Error	90% Confidence Intervals
CP-866,087 1 mg	21	1.33	0.22	0.34	-0.34, 0.79
CP-866,087 3 mg	21	0.76	-0.34	0.34	-0.92. 0.23
CP-866,087 10 mg	22	0.86	-0.24	0.34	-0.81, 0.33
Placebo	32	1.10	N/A	N/A	N/A

Score range: 2-10, where 2 indicates the worst response and 10 indicates the best response.
AFSQ = Abbreviated Sexual Function Questionnaire, ANOVA = analysis of variance, PPAS = per protocol analysis set.

Table 6. ANOVA results for Change From Baseline for ASFQ Arousal-Sensation Domain (PPAS)

Treatment	Number of Subjects	Least Squares Mean Estimate	Difference From Placebo		
			Least Squares Mean Estimate	Standard Error	90% Confidence Intervals
CP-866,087 1 mg	21	1.66	0.54	0.73	-0.68, 1.76
CP-866,087 3 mg	21	0.64	-0.47	0.74	-1.71, 0.76
CP-866,087 10 mg	22	1.18	0.07	0.77	-1.22, 1.35
Placebo	32	1.11	N/A	N/A	N/A

Score range: 4-20, where 4 indicates the worst response and 20 indicates the best response.
ASFQ = Abbreviated Sexual Function Questionnaire, ANOVA = analysis of variance, PPAS = per protocol analysis set.

Table 7. ANOVA results for Change From Baseline for ASFQ Desire Domain (PPAS)

Treatment	Number of Subjects	Least Squares Mean Estimate	Difference From Placebo		
			Least Squares Mean Estimate	Standard Error	90% Confidence Intervals
CP-866,087 1 mg	21	2.77	0.76	0.78	-0.54, 2.06
CP-866,087 3 mg	21	1.73	-0.28	0.78	-1.59, 1.03
CP-866,087 10 mg	22	1.71	-0.30	0.77	-1.60, 0.99
Placebo	32	2.01	N/A	N/A	N/A

Score range: 5-31, where 5 indicates the worst response and 31 indicates the best response.
ANOVA = analysis of variance, ASFQ = Abbreviated Sexual Function Questionnaire, PPAS = per protocol analysis set.

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Table 8. ANOVA results for Change From Baseline for Sexual Activity Satisfaction Score (PPAS)

Treatment	Number of Subjects	Least Squares Mean Estimate	Difference From Placebo		
			Least Squares Mean Estimate	Standard Error	90% Confidence Intervals
CP-866,087 1 mg	21	0.40	0.31	0.21	-0.04, 0.66
CP-866,087 3 mg	21	0.20	0.11	0.21	-0.24, 0.46
CP-866,087 10 mg	22	-0.05	-0.15	0.19	-0.48, 0.18
Placebo	32	0.09	NA	NA	NA

Score range for change from Baseline: -4 (worst) to +4 (better).
ANOVA = analysis of variance, PPAS = per protocol analysis set.

Safety Results:

The incidence of all causality treatment-emergent AEs (treatment-related) for ≥2 subjects is reported in Table 9. The most commonly reported all causality AEs were nausea, which was reported by 1, 5 and 6 subjects for 1, 3 and 10 mg CP-866,087 treatment groups, respectively (4 subjects on placebo) and fatigue, which was reported by 1, 2 and 3 subjects in the 1, 3 and 10 mg CP-866,087 treatment groups, respectively (3 subjects on placebo).

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Table 9. Incidence of All Causality Treatment-Emergent Adverse Events (Treatment-Related) ≥2 Subjects

System Organ Class and MedDRA (v11.1) Preferred Term	CP-866,087			Placebo N=32
	1 mg N=21	3 mg N=21	10 mg N=22	
Nausea	1 (1)	5 (4)	6 (5)	4 (2)
Fatigue	1 (1)	2 (2)	3 (3)	3 (3)
Diarrhea	1 (1)	1 (0)	2 (1)	2 (0)
Headache	1 (1)	1 (1)	2 (1)	2 (1)
Gastroenteritis	1 (0)	0	2 (0)	1 (0)
Dry eye	1 (0)	0	2 (2)	0
Somnolence	0	0	2 (0)	1 (0)
Nasopharyngitis	0	1 (0)	1 (0)	2 (0)
Upper respiratory tract infection	2 (0)	0	1 (0)	1 (0)
Dysmenorrhea	1 (1)	2 (2)	0	1 (1)
Flushing	0	2 (2)	0	2 (2)
Pharyngitis	2 (0)	0	0	3 (0)
Pharyngitis streptococcal	2 (0)	0	0	0
Alanine aminotransferase increased	2 (1)	0	0	1 (1)

MedDRA = Medical Dictionary of Regulatory Activities, N = number of subjects per treatment group, v = version.

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One (1) subject experienced a serious adverse event (cholelithiasis) following treatment with CP-866,087 10 mg, which was not considered related to the study treatment by the Investigator and Sponsor. A total of 7 subjects permanently discontinued due to AEs and all the discontinuations were found to be related to the study treatment except 1 subject as shown in Table 5.

Table 10. Permanent Discontinuations due to Adverse Events

Serial Number	Age	MedDRA Preferred Term (v11.1)	Treatment at Onset	Severity	Outcome	Treatment-Related	SAE
1	24	Constipation	CP-866,087 1 mg	Moderate	Recovered	Yes	No
2	25	Cervix Dysplasia	CP-866,087 3 mg	Severe	Recovered	No	No
3	31	Nausea	CP-866,087 10 mg	Severe	Recovered	Yes	No
4	27	Lethargy	CP-866,087 10 mg	Moderate	Recovered	Yes	No
5	23	Nausea	Placebo	Moderate	Recovered	Yes	No
		Asthenia	Placebo	Moderate	Recovered	Yes	No
		Headache	Placebo	Moderate	Recovered	Yes	No
		Tremor	Placebo	Moderate	Recovered	Yes	No
6	30	Fatigue	Placebo	Mild	Recovered	Yes	No
7	21	Fatigue	Placebo	Mild	Recovered	Yes	No

MedDRA = Medical Dictionary of Regulatory Activities, SAE = serious adverse event, v = version.

Eight (8) subjects temporarily discontinued study due to AEs as shown in Table 11.

Table 11. Temporary Discontinuations due to Adverse Events

Serial Number	Age	MedDRA Preferred Term (v11.1)	Treatment at Onset	Severity	Outcome	Treatment-Related	Serious Adverse Event
1	25	Pharyngitis	CP-866,087 1 mg	Mild	Recovered	No	No
2	39	Tendonitis[a]	CP-866,087 1 mg	Moderate	Recovered	No	No
		Tendonitis[a]	Placebo	Moderate	Recovered	No	No
3	31	Influenza	CP-866,087 1 mg	Mild	Recovered	No	No
4	31	Tonsillitis	CP-866,087 3 mg	Severe	Recovered	No	No
5	28	Extrasystoles	CP-866,087 3 mg	Mild	Recovered	Yes	No
		Palpitations	CP-866,087 3 mg	Mild	Recovered	Yes	No
		Dizziness	CP-866,087 3 mg	Moderate	Recovered	Yes	No
6	26	Oesophagitis	CP-866,087 10 mg	Moderate	Recovered	Yes	No
7	30	Vomiting	CP-866,087 10 mg	Moderate	Recovered	No	No
		Somnolence	Placebo	Moderate	Recovered	Yes	No
8	25	Urticaria	Placebo	Mild	Recovered	No[a]	No

MedDRA = Medical Dictionary of Regulatory Activities, v = version.
a. Adverse event was attributed to concomitant medication and was not treatment-emergent.

There were no deaths reported during this study.

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Eleven (11) subjects reported laboratory test abnormalities from normal baseline for CP-866,087 and placebo but they were not considered to be clinically significant and there were no trends across any given body system. One (1) subject reported a laboratory test abnormality from abnormal baseline but it was not considered clinically significant. Three (3) subjects were reported to have clinically significant changes from Baseline, but none were classified as AEs. One (1) subject in the CP-866,087 10 mg treatment group and 1 subject in the placebo group showed a maximum QTcB interval (Bazett's correction) increase from Baseline of 30≤ change <60 msec, and 1 subject in the placebo group showed a maximum QTcF interval (Fridericia's correction) increase from Baseline of 30≤ change <60 msec.

CONCLUSIONS:

Based on the efficacy endpoints, there was no clinical treatment benefit for CP-866,087 at the doses studied (1, 3 and 10 mg) in this population of women. The type and incidence of AEs reported are consistent with this class of compounds and were similar to those observed in previous studies conducted with CP-866,087. Overall, the incidence of all causality AEs was relatively low across all treatment groups with slightly higher incidences occurring in the CP-866,087 10 mg group. For the comparison of each dose of CP 866,087 against placebo, the 90% CIs for all the efficacy variables presented, included 0. None of these 90% CIs included the MCID for the ASFQ endpoints. Furthermore, the %SSE endpoint, which was considered a key endpoint for regulatory considerations, showed no meaningful difference between treatment groups.

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