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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Alesse® / Levonorgestrel / Ethinyl Estradiol

PROTOCOL NO.: 0858A4-318-WW (B3121030)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of a Combination of Levonorgestrel and Ethinyl Estradiol in a Continuous Daily Regimen in Subjects With Premenstrual Dysphoric Disorder

Study Centers: A total of 41 centers screened subjects of which 23 centers randomized subjects: 6 in Germany; 4 in Finland, 3 in Sweden, 1 each in South Africa, Chile and United Kingdom (UK), 5 in Poland, and 2 in Romania.

Study Initiation and Final Completion Dates: 19 September 2005 to 05 December 2007

Phase of Development: Phase 3

Study Objectives:

Primary Objectives: There were 4 co-primary endpoints, each of which was based on comparison between the levonorgestrel (LNG) 90 μg/ethinyl estradiol (EE) 20 μg continuous regimen and placebo groups, of the mean change from the Baseline efficacy period in average Daily Record of Severity of Problems (DRSP) 21-item total daily scores. The 4 comparisons of primary interest were the changes between baseline and: (1) Cycle 1 efficacy period; (2) the worst 5 days during Cycle 1; (3) the last on-therapy efficacy period; and (4) the worst 5 days during the last on-therapy estimated cycle.

Secondary Objectives: The secondary objectives were to evaluate the effect of treatment with LNG 90 μg/EE 20 μg administered in a continuous daily regimen versus that of placebo on the following:

- Analysis of DRSP scores averaged over the study;
- Responder/remitter analyses based on Clinical Global Impression - Severity (CGI-S) scores, percentage improvement in DRSP scores, and premenstrual dysphoric disorder (PMDD) criteria;
- CGI-S scores;
- Change from Baseline in mean clinically defined DRSP cluster (symptom subgroup) scores;

- Change from Baseline in Work Limitations Questionnaire (WLQ);
- Subject global evaluation (SGE), mean scores;
- Change in body weight.

METHODS

Study Design: This was a Phase 3, multicenter, randomized, double-blind, and placebo-controlled study of a combination of LNG and EE in a continuous daily regimen in subjects with PMDD. The first 2 cycles of the study were pretreatment screening cycles, followed by 1 cycle of single-blind placebo run-in treatment (Table 1), followed by active double-blind treatment with four 28-day tablet-in-capsule (TIC) packs (pill packs), followed by a posttreatment visit.

Table 1. Schedule of Activities

	Pretreatment Screening			Single-Blind Placebo Run-In	Double-Blind Treatment Interval					Posttreatment
Visit	**1**	**2[a]**	**3**		**4**	**5**	**6**	**7**	**8**	**9[b]**
Cycle/TIC Pack	**1**	**2**		**3**	**4**		**5**	**6**	**7**	**8**
Days	**4-35[c]**	**8-12[c]**	**Efficacy Period[d]**	**1-35**	**1-5[c]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**1-15**
Informed consent	X									
Medical history	X									
Weight/sitting blood pressure/height at Visit 1	X	X	X		X	X	X	X	X	X
Urine pregnancy test[e]	X		X		X	X	X	X	X	X
Inclusion/exclusion criteria	X	X	X		X				X	X
Fasting laboratory safety screen[f]	X									
TSH	X									
Physical and neurological exam	X									X
Gynecological exam	X									X
Cervical cytological smear/HPV as needed[g]	X									X
Mammogram (if needed)[h]	X									
MINI for DSM-IV Axis I disorders		X								
Administer HAM-D_{17}		X								
Assess CGI–S			X			X	X	X	X	
Administer subject global evaluation						X	X	X	X	
Dispense AE/bleeding diary cards[i]	2									
Dispense daily diaries[j]			2			1	1	1		
Dispense DRSP[k]	1		2			1	1	1		
Collect DRSP					2		1	1	1	1
Assess					X					
DRSP/randomization[l]										
Dispense WLQ[m]	2		3		3	2	2	2		
Collect AE/bleeding diary cards		1			1					
Collect daily diary cards					1		1	1	1	1
Collect WLQ					5	1	2	2	4	

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Cycle/TIC Pack	**1**	**2**		**3**	**4**		**5**	**6**	**7**	**8**
Days	**4-35[c]**	**8-12[c]**	**Efficacy Period[d]**	**1-35**	**1-5[c]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**1-15**
Dispense test article/TIC packs[n]			2		1[o]	1	1	1		
Collect test article/TIC packs					2		1	1	1	1
Assess tobacco use and back-up contraception	X	X	X			X	X	X	X	X
Assess adverse events	X----------									----------X

AE = adverse event; ASCUS = atypical squamous cells of undetermined significance; CGI-S = Clinical Global Impression scale-Severity of Illness item; DRSP = Daily Record of Severity of Problems; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HAM-D_{17} = Hamilton Depression Rating Scale, 17-item; HPV = human papilloma virus; MINI = mini international neuropsychiatric interview; TIC = tablet-in-capsule; TSH = thyroid-stimulating hormone; WLQ = Work Limitations Questionnaire.

a. Results from Visit 1 testing must have been available by Visit 2 or the subject was considered a screen failure.
b. Posttreatment Visit 9 was to occur between Days 1 and 15 after last dose of test article. Any remaining TIC packs and diaries were to be returned to the site at this visit.
c. Pretreatment screening Visit 1 was to occur anytime during the subject's Cycle 1 but after menses so that a cervical cytological smear could be adequately obtained. Pretreatment screening Visit 2 was to occur during the subject's follicular phase of Cycle 2. Double-blind treatment interval Visit 4 was to occur as soon after Day 1 (onset of her menstrual period) as possible, not to exceed Day 5 of Cycle 4. Every effort was to be made to conduct the visit during the time frame described, but some flexibility was permitted to accommodate individual cycle length and scheduling logistics.
d. Pretreatment screening Visit 3 was to coincide with the subject's efficacy period (the 6 days before menses through Day 1 of menses [7 days total]) in Cycle 2 in so far as possible. Double-blind treatment interval Visits 5, 6, 7, and 8 were to occur during Days 22 through 28 of each TIC pack.
e. Serum β-human chorionic gonadotropin analysis was to be performed for subjects who had a positive urine pregnancy test result.
f. Subjects were to fast for at least 12 hours before phlebotomy at pretreatment screening Visit 1, double-blind treatment interval Visit 8, and posttreatment Visit 9.
g. Subjects must have had a cervical cytological smear report of negative for intraepithelial lesion or malignancy. If ASCUS was reported at Screening, the subject must have had a negative test for HPV. The cervical cytological smear must have been performed at pretreatment screening Cycle 1 (Visit 1) or within 6 months before Visit 1 provided that a copy of the report was available. The cervical cytological smear was also to be performed at Visit 9. If ASCUS was reported at this time, the sample was to be tested for HPV.
h. A mammogram was required for subjects who were ≥40 years of age at pretreatment screening Cycle 1 (Visit 1) or who would become 40 during the course of the study. A mammogram within 6 months of Visit 1 was acceptable for these subjects provided a copy of the report was obtained and the results were recorded on the case report form.
i. An AE diary card was to be dispensed for the assessment of AEs (symptoms and complaints), method of contraception, and tobacco use during Cycle 1. An AE/bleeding diary card was to be dispensed for the assessment of AEs (symptoms and complaints) method of contraception, tobacco use, and bleeding during Cycle 2.
j. Diary cards were to be dispensed to document the occurrence of AEs (symptoms and complaints), method of contraception, tobacco use, bleeding, and test article use. After randomization, subjects were to begin completing a new diary with each TIC pack
k. DRSPs were to be dispensed at pretreatment screening Visits 1 and 3 and at double-blind treatment interval Visits 5, 6, and 7. After randomization, subjects were to begin completing a new DRSP with each TIC pack.
l. DRSP scores were to be assessed to evaluate eligibility. If the subject continued to meet severity/eligibility criteria, the subject was then randomly assigned to double-

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Cycle/TIC Pack	**1**	**2**		**3**	**4**		**5**	**6**	**7**	**8**
Days	**4-35[c]**	**8-12[c]**	**Efficacy Period[d]**	**1-35**	**1-5[c]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**22-28[d]**	**1-15**

blinded test article during cycle Days 1 through 5 of Cycle 4 after the placebo run-in phase.

m. WLQs were to be dispensed to subjects who received pay for work at pretreatment screening Visits 1 and 3 and double-blind treatment interval Visits 4, 5, 6, and 7. Subjects completed the WLQs (on Days 1 and 12) during the pretreatment screening Cycle 2, single-blind placebo run-in Cycle 3, double-blind treatment interval Cycle 4, and on "estimated" Days 1 and 12 of subsequent double-blind treatment cycles. More blank WLQs than may be needed will be dispensed to ensure an adequate supply between visits.

n. Two (2) single-blind placebo run-in TIC packs dispensed at pretreatment screening Cycle 2 (Visit 3). Each subject was to begin single-blind, placebo run-in test article on the first day of her menstrual bleeding during single-blind placebo run-in Cycle 3. Each single-blind pill pack contained 28 TICs each of placebo to match LNG 90 µg/EE 20 µg. Each subject received enough placebo run-in test article to take 1 TIC daily, orally, for the duration of that cycle. Subjects were to be instructed to stop taking single-blind, placebo run-in test article beginning on Day 1 (onset of the menstrual period) of their next menstrual cycle (double-blind treatment interval Cycle 4). Double-blind test article was dispensed at double-blind treatment interval Visits 4, 5, 6, and 7.

o. During double-blind treatment interval Cycle 4, subjects were to begin double-blind test article as soon after Day 1 (onset of the menstrual period) as possible, not to exceed Day 5 of Cycle 4. Each subject was instructed to take 2 TICs of double-blind test article daily until the subject had consumed the appropriate amount of medication for her day in the cycle.

Number of Subjects (Planned and Analyzed): Approximately 90 subjects were planned to be randomly assigned to receive LNG 90 µg/EE 20 µg or placebo; 104 subjects were randomly assigned to study drug (47 to LNG 90 µg/EE 20 µg and 57 to placebo). Four (4) subjects (1 assigned to LNG 90 µg/EE 20 µg and 3 assigned to placebo) never took study drug. During the double-blind study interval, 46 subjects received at least 1 dose of LNG 90 µg/EE 20 µg and 54 subjects received placebo.

Diagnosis and Main Criteria for Inclusion: Female subjects aged 18 to 49 years, who met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for PMDD and who were willing to take a combination oral contraceptive were included in the study. Symptoms consistent with PMDD must have been present over the past year, occurring during the last week of the late luteal phase in most menstrual cycles, beginning to remit within a few days of the onset of menses (the follicular phase), and absent in the week following menses. Subjects must prospectively have met the following criteria using the DRSP instrument and worksheet: had an average (across 5 days) daily follicular phase (Days 8 to 12 after the first day of menses) score < 3 on each of the 21 items during both the pretreatment screening Cycle 2 and placebo run-in Cycle 3; had each qualifying symptom on at least 4 of 7 efficacy period days (the 6 days before menses through Day 1 of menses [7 days total]); not be at risk for pregnancy during the study or using an effective, nonhormonal method of birth control. Subjects must have had regular (21- to 35-day) menstrual cycles by history for the 2-month period preceding the pretreatment screening Cycle 1 (Visit 1).

Exclusion Criteria: Subjects had major depressive disorders requiring antidepressant treatment or hospitalization, or associated with suicide attempt or risk for suicide within the last 3 years before pretreatment screening Cycle 1 (Visit 1) or seasonal affective disorders, bipolar depression, psychotic disorders, somatoform disorders, dysthymic disorders, schizophrenia, obsessive-compulsive disorders, or antisocial/ borderline/schizotypal personality disorders were excluded from the study.

Study Treatment: Subjects received oral daily doses of LNG 90 µg/EE 20 µg, or placebo, 1 TIC. Each subject was to begin single-blind, placebo run-in test article on the first day of her menstrual bleeding during single-blind placebo run-in Cycle 3. Subjects were instructed to stop taking single-blind, placebo run-in test article on Day 1 (onset of her menstrual period) of her next menstrual cycle (double-blind treatment Cycle 1, study Cycle 4). After the placebo run-in phase, if the subject continued to meet severity/eligibility criteria, she was then randomly assigned to double-blind treatment group as shown in Table 2 and took double-blind test article during Days 1 through 5 of study Cycle 4.

Table 2. Double-Blind Treatment Groups

Group	Treatment
A	Double-blind combination TIC containing LNG 90 µg and EE 20 µg
B	Placebo to match double-blind combination TIC containing LNG 90 µg and EE 20 µg

EE = ethinyl estradiol; LNG = levonorgestrel; TIC = tablet in capsule.

Subjects were to take 2 TICs of double-blind test article daily until the subject had consumed the appropriate amount of medication for her day in the cycle. With the exception of the beginning of Cycle 4, subjects took 1 TIC daily, orally, for approximately 112 days at approximately the same time each day.

Efficacy Endpoints:

Primary Endpoints: The 4 co-primary endpoints were based on comparison of LNG 90 µg/EE 20 µg double-blind treatment to placebo for the mean change in average total DRSP 21-item daily scores. The 4 comparisons of primary interest were the changes between baseline and:

- The Cycle 1 efficacy period;
- The worst 5 days during Cycle 1;
- The last on-therapy efficacy period, and;
- The worst 5 days during the last on-therapy cycle.

Secondary Endpoints: The secondary endpoints were to evaluate the effect of treatment with LNG/EE administered in a continuous daily regimen versus placebo on the following:

- Analysis of DRSP scores averaged over the study;
- Responder/remitter analyses based on CGI-S scores, percentage improvement in DRSP scores and PMDD criteria;
- CGI-S scores;
- Change from Baseline in mean clinically defined DRSP cluster (symptom subgroup) scores;
- Change from Baseline in WLQ;
- Subject global evaluation mean scores;
- Change in weight.

Safety Evaluations: Safety was evaluated primarily from adverse events (AEs) recorded on diary cards or reported to study personnel. In addition, physical and gynecologic examinations, vital sign measurements, and clinical laboratory determinations were performed during the study.

Statistical Methods: The following analysis population sets were used in this study:

- Change From Baseline DRSP Score: Subjects meeting the following criteria were used in each DRSP change from Baseline analysis.
    - All randomized subjects with DRSP data for at least 5 of the 7 efficacy period days who completed both Cycles 2 and 3 (for baseline) and had sufficient on-therapy

data were included in the DRSP efficacy period analysis for each "estimated" on-therapy cycle;

- Subjects with DRSP data for at least 5 of the 7 efficacy period days who completed both Cycles 2 and 3 (for baseline) and at least 1 on-therapy cycle were included in the DRSP efficacy period analysis for last on-therapy "estimated" cycle. The last cycle with sufficient data was be used for each subject;

- Subjects with DRSP data for at least 5 of the 7 efficacy period days who completed both Cycles 2 and 3 (for baseline) and qualified for the late luteal efficacy period analysis for "estimated" Cycle 1 were included in the DRSP "worst 5 days" analysis.

- Average DRSP Score Over the Study: Data from all randomized subjects who were in the double-blind portion of the study for at least 1 "estimated" cycle were included in the analysis of DRSP scores using average score throughout the study.

- Responder and Remitter Analyses:

  - Responder: A responder was defined as a subject whose DRSP 21-item efficacy period average daily score improved by ≥50%, with a CGI-S improvement of ≥1. All randomized subjects with baseline and double-blind on-therapy values for the DRSP during the late luteal phase and a CGI-S score within the same estimated cycle were included in the responder analysis.

  - Remitter: A subject was considered in remission if she was a responder and, at the end of her participation in the study, she no longer met the PMDD entry criteria with respect to the DRSP. All randomized subjects with at least 1 double-blind on-therapy cycle with data for the DRSP during the follicular and late luteal phases and a CGI-S score within the same estimated cycle were included in the remitter analysis.

- WLQ: All subjects who received pay for work were to complete the WLQ questionnaire. Randomized subjects having both screening and on-therapy data for Day 1 (which refers to the estimated premenstrual week) were included in the analysis for each estimated cycle.

- CGI-S and Subject Global Evaluation: For CGI-S, randomly assigned subjects with baseline and at least 1 double-blind on-therapy observation were included in the analysis. Because the SGE had no baseline record, randomly assigned subjects with at least 1 double-blind on-therapy observation were included in the analysis.

- Safety Population: All subjects who received at least 1 dose of study medication were to be included in the analyses of safety data.

The 4 co-primary efficacy endpoints included the comparison of treatment groups on mean change in average DRSP 21-item total daily scores, from the Baseline (late luteal) efficacy

period to the "estimated" on-therapy Cycle 1 (late luteal) efficacy period and also from the Baseline (late luteal) efficacy period to "estimated" on-therapy Cycle 1 using the "worst 5 days" (regardless of when in Cycle 1 they occurred). The last on-therapy "estimated" cycle was also to be analyzed for each of these measures. Secondary efficacy evaluations included analysis of DRSP scores averaged over the study, responder and remitter analyses, and additional supportive analyses of the other secondary efficacy endpoints.

RESULTS

Subject Disposition and Demography: Of the 629 subjects screened, 525 subjects were screen failures, with 104 subjects randomly assigned to study drug (47 to LNG 90 µg/EE 20 µg and 57 to placebo); 4 subjects (1 assigned to LNG 90 µg/EE 20 µg and 3 assigned to placebo) never took study drug. During the double-blind study interval, 46 subjects received at least 1 dose of LNG 90 µg/EE 20 µg and 54 subjects received placebo. Overall, 15 (32.6%) LNG 90 µg/EE 20 µg subjects and 8 (14.8%) placebo subjects discontinued from the study. The primary reasons for these discontinuations are summarized in Table 3.

Table 3. Number (%) of Subjects Who Completed or Discontinued Study by Primary Reason

Conclusion Status Reason[a]	Overall p-Value	Treatment	
		LNG 90 µg/EE 20 µg n=46	Placebo n=54
Total		46 (100)	54 (100)
Completed	0.055	31 (67.4)	46 (85.2)
Study completed	0.055	31 (67.4)	46 (85.2)
Discontinued	0.055	15 (32.6)	8 (14.8)
Adverse event	0.042*	4 (8.7)	0
Lost to follow-up	1.000	1 (2.2)	1 (1.9)
Protocol violation	0.465	5 (10.9)	3 (5.6)
Subject request	0.729	5 (10.9)	4 (7.4)

Overall p-value: Fisher exact test p-value (2-tail).
Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.
EE = ethinyl estradiol; LNG = levonorgestrel; n = number of subjects.
a. Total discontinued is the sum of individual reasons because they were mutually exclusive by subject.

The demographic and baseline characteristics for subjects randomly assigned to LNG 90 µg/EE 20 µg or placebo who took at least 1 dose of study drug are summarized by treatment group in Table 4.

Table 4. Demographic and Baseline Characteristics

Characteristic Value	p-Value	Treatment LNG 90 µg/EE 20 µg (N=46)	 Placebo (N=54)	 Total (N=100)
Age (year)				
Mean	0.858[a]	36.28	36.57	36.44
Standard deviation		8.36	7.91	8.08
Minimum - maximum		18 – 49	18 - 49	18 - 49
Race				
White		46 (100)	54 (100)	100 (100)
Ethnicity	0.187[b]			
Hispanic or Latino		0	2 (3.70)	2 (2.00)
Non-Hispanic and Non-Latino		46 (100)	52 (96.30)	98 (98.00)
Height (cm)				
Mean	0.248[a]	167.07	168.43	167.80
Standard deviation		5.28	6.26	5.84
Minimum - maximum		155 - 178	156 - 182	155 - 182
Weight (kg)				
Mean	0.326[a]	67.42	70.11	68.87
Standard deviation		12.56	14.39	13.58
Minimum – maximum		51.0 - 105.8	48.2 - 105.5	48.2 - 105.8
BMI (kg/m^2)				
Mean	0.561[a]	24.12	24.62	24.39
Standard deviation		4.18	4.40	4.29
Minimum –maximum		18.58 – 38.39	18.37 – 37.47	18.37 - 38.39
Duration on therapy (days)				
Mean	0.067[a]	91.85	101.89	97.27
Standard deviation		31.63	22.35	27.34
Minimum – maximum		14 - 115	22 - 114	14 - 115
Study completed	0.035[b]			
No		15 (32.61)	8 (14.81)	23 (23.00)
Yes		31 (67.39)	46 (85.19)	77 (77.00)
Primary diagnosis				
Premenstrual dysphoric disorder		46 (100)	54 (100)	100 (100)
Smoke cigarettes	0.367[b]			
No		38 (82.61)	48 (88.89)	86 (86.00)
Yes		8 (17.39)	6 (11.11)	14 (14.00)
Cigarettes smoked per day (smokers)				
n		46	53	99
Mean	0.607[a]	1.30	0.97	1.13
Standard deviation		3.20	3.21	3.19
Minimum – maximum		0 – 10	0 – 15	0 – 15
Missing		0	1	1

BMI = body mass index; EE = ethinyl estradiol; LNG = levonorgestrel; N = total number of subjects; n = number of subjects of subjects with prespecified criteria.
a. One-way analysis of variance with treatment as factor.
b. p-Value for Chi-Square.

Efficacy Results:

Primary Endpoints:

Adjusted Changes in Daily Record of Severity of Problems From Baseline During the Late Luteal Efficacy Period: The adjusted change in DRSP 21-item total daily scores from Baseline to the late luteal efficacy period are shown by estimated cycle, and to the last on-therapy cycle in Table 5.

Table 5. DRSP 21-Item Scores During the Late Luteal Efficacy Period: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	Number of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-24.79	3.29	<.001	0.488
	2	37	-41.65	2.95	<.001	<.001
	3	34	-42.40	3.15	<.001	0.007
	4	14	-37.09	5.51	<.001	0.844
	Last on therapy	41	-39.30	2.92	<.001	0.199
Placebo	1	52	-21.85	2.86	<.001	
	2	50	-27.44	2.44	<.001	
	3	46	-31.75	2.59	<.001	
	4	20	-35.84	4.03	<.001	
	Last on therapy	52	-34.45	2.53	<.001	

p-Values based on ANCOVA model: change = site + treatment + average baseline cycle length +baseline value.
ANCOVA = analysis of covariance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = Levonorgestrel; SE = standard error; vs = versus.

The mean total daily scores during the late luteal efficacy period decreased significantly in both groups during the first double-blind estimated cycle but there was no difference between the LNG 90 µg/ EE 20 µg and placebo groups. The adjusted change during the last on-therapy cycle was somewhat greater in the LNG 90 µg/EE 20 µg group than in the placebo group, although the difference was not significant. During the second and third double-blind estimated cycles, the adjusted change was significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group.

Adjusted Changes in Daily Record of Severity of Problems From Baseline During the Worst 5 Days: The adjusted mean change in DRSP 21-item total daily score from the late luteal efficacy period at Baseline during the worst 5 days with the highest DRSP scores during each estimated cycle are shown by estimated cycle and last on-therapy cycle in Table 6.

Table 6. DRSP 21-Item Scores During the Worst 5 Days: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	Number of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-16.15	2.76	<.001	0.381
	2	37	-29.46	2.94	<.001	0.006
	3	34	-31.83	3.08	<.001	0.003
	4	14	-26.16	7.09	<.001	0.954
	Last on therapy	41	-30.44	2.91	<.001	0.061
Placebo	1	52	-13.03	2.40	<.001	
	2	50	-19.09	2.44	<.001	
	3	46	-20.54	2.53	<.001	
	4	20	-25.69	5.19	<.001	
	Last on therapy	52	-23.34	2.52	<.001	

p-Values based on ANCOVA model: change = site + treatment + average baseline cycle length +baseline value.
ANCOVA = analysis of covariance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = Levonorgestrel; SE = standard error; vs = versus.

The mean total daily scores during the worst 5 days during the first double-blind estimated cycle decreased significantly in both groups from Baseline efficacy period scores but there was no difference between the LNG 90 µg/EE 20 µg and placebo groups. The adjusted change at the last on-therapy cycle was somewhat greater in the LNG 90 µg/EE 20 µg group than in the placebo group, although the difference was not significant. During the second and third double-blind estimated cycle, the adjusted mean decreases were significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group.

Secondary Endpoints:

Analysis of DRSP Scores Using Average Throughout the Study: The average of a subject's 21-item total DRSP scores for each day was taken across all available days on double-blind therapy throughout the study and summarized by treatment group (Table 7). Overall, there was no difference seen between groups.

Table 7. Average 21-Item DRSP Scores Over Study: Comparisons Within and Between Groups

Treatment	N	Adjusted Change		p-Value Within Group	p-Value vs Placebo
		Mean	SE		
LNG 90 µg/EE 20 µg	42	33.11	1.32	<.001	0.153
Placebo	52	35.59	1.18	<.001	

p-Values based on ANOVA model: score = site + treatment.
ANOVA = analysis of variance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; N = number of subjects in each treatment group; SE = standard error; vs = versus.

Responder Analysis: Subjects with baseline and double-blind on-therapy values for the 21-item DRSP during the late luteal phase and CGI-S during the same estimated cycle were

included in the responder analysis. Subjects whose DRSP average daily score improved by ≥50% and CGI-S improved by ≥1 are summarized by treatment group in Table 8.

Table 8. Number (%) of Responders: Comparisons Between Groups

Double-Blind Estimated Cycle	Treatment	No. of Responders	Total	Response %	p-Value vs Placebo
1	LNG 90 µg /EE 20 µg	8	34	23.53	0.572
	Placebo	8	49	16.33	
2	LNG 90 µg /EE 20 µg	16	32	50.00	0.033
	Placebo	12	47	25.53	
3	LNG 90 µg /EE 20 µg	22	34	64.71	0.022
	Placebo	16	43	37.21	
4	LNG 90 µg /EE 20 µg	6	10	60.00	>0.999
	Placebo	10	16	62.50	
Last on therapy	LNG 90 µg /EE 20 µg	24	40	60.00	0.059
	Placebo	20	51	39.22	

Response is defined as at least 50% improvement from Baseline in late luteal DRSP score and a CGI-S improvement of ≥1.
Last on therapy is each subject's last estimated double-blind cycle with both late luteal DRSP data and a CGI-S value.
p-Value obtained from Fisher exact test.
CGI-S = Clinical Global Impression Scale‑Severity of Illness; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; vs = versus.

In double-blind estimated Cycles 2 and 3, significantly more subjects in the LNG 90 µg/EE 20 µg group were responders than in the placebo group. During the last on-therapy cycle, 60% of subjects in the LNG 90 µg/EE 20 µg group were responders, compared with 39% in the placebo group, although this difference was not statistically significant.

Remitter Analysis: Although the percentage of remitters in the LNG 90 µg/EE 20 µg group was greater than in the placebo group, this difference was not statistically significant (Table 9).

Table 9. Number (%) of Remitters: Comparisons Between Groups

Time	Treatment	No. of Remitters	Total	Remitter %	p-Value vs Placebo
Last on therapy	LNG 90 µg /EE 20 µg	21	40	52.50	0.289
	Placebo	20	51	39.22	

Remitter is defined as a responder whose last on-therapy met the relevant inclusion criteria.
Last on therapy is each subject's last estimated double-blind cycle with both late luteal DRSP data and a CGI-S value.
p-Value obtained from Fisher exact test.
CGI-S = Clinical Global Impression Scale‑Severity of Illness; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; vs = versus.

Change From Baseline in DRSP Cluster Scores: The change in average daily score over the 5 most symptomatic efficacy period days for the items specific to each cluster were

compared between the treatment groups using analysis of covariance (ANCOVA). If any of the items in a cluster were missing, the data for that day were not used.

DRSP Depressive Symptoms: The adjusted mean change in the depressive symptom DRSP cluster scores are summarized by double-blind estimated cycle and compared between treatment groups in Table 10.

Table 10. DRSP Scores for the Depressive Cluster During the Late Luteal Efficacy Period: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	No. of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-6.71	0.96	<.001	0.694
	2	37	-11.65	0.87	<.001	<.001
	3	34	-11.78	0.93	<.001	0.011
	4	14	-9.53	1.53	<.001	0.841
	Last on therapy	41	-10.82	0.84	<.001	0.167
Placebo	1	52	-6.22	0.83	<.001	
	2	50	-7.40	0.72	<.001	
	3	46	-8.86	0.76	<.001	
	4	20	-9.17	1.09	<.001	
	Last on therapy	52	-9.31	0.73	<.001	

Cluster includes relevant individual inclusion criteria.
p-Values based on ANCOVA model: change = site + treatment + baseline value.
ANCOVA = analysis of covariance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; SE = standard error; vs = versus.

The improvement seen in the depressive symptom scores was significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group at double-blind estimated Cycles 2 and 3.

DRSP Physical Symptoms: The adjusted mean change in the physical symptom DRSP cluster scores are summarized by double-blind estimated cycle and compared between treatment groups in Table 11.

Table 11. DRSP Scores for the Physical Symptom Cluster During the Late Luteal Efficacy Period: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	No. of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-3.92	0.64	<.001	0.755
	2	37	-6.95	0.60	<.001	0.003
	3	34	-7.51	0.57	<.001	0.001
	4	14	-5.99	1.17	<.001	0.550
	Last on therapy	41	-6.54	0.57	<.001	0.233
Placebo	1	52	-3.66	0.57	<.001	
	2	50	-4.68	0.50	<.001	
	3	46	-5.14	0.47	<.001	
	4	20	-5.19	0.79	<.001	
	Last on therapy	52	-5.66	0.50	<.001	

Cluster includes relevant individual inclusion criteria.
p-Values based on ANCOVA model: change = site + treatment + baseline value.
ANCOVA = analysis of covariance; DRS = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; SE = standard error; vs = versus.

The improvement seen in the physical symptom scores was significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group at double-blind estimated Cycles 2 and 3.

DRSP Anger or Irritability: The adjusted mean change in the anger or irritability symptom DRSP cluster scores are summarized by double-blind estimated cycle and compared between treatment groups in Table 12.

Table 12. DRSP Scores for the Anger or Irritability Cluster During the Late Luteal Efficacy Period: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	No. of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-2.91	0.39	<.001	0.363
	2	37	-4.49	0.38	<.001	0.001
	3	34	-4.58	0.35	<.001	0.014
	4	14	-4.64	0.66	<.001	0.567
	Last on therapy	41	-4.20	0.34	<.001	0.380
Placebo	1	52	-2.45	0.34	<.001	
	2	51	-2.92	0.31	<.001	
	3	46	-3.52	0.29	<.001	
	4	20	-4.21	0.44	<.001	
	Last on therapy	52	-3.81	0.30	<.001	

Cluster includes relevant individual inclusion criteria.
p-Values based on ANCOVA model: change = site + treatment + baseline value.
ANCOVA = analysis of covariance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; SE = standard error; vs = versus.

The improvement seen in the anger or irritability symptom scores was significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group at double-blind estimated Cycle 2 and 3.

DRSP Minimum Clinically Important Difference: For the 19 women who reported feeling slightly better or slightly worse (score of –1 or +1) on the SGE during their last on-therapy estimated cycle, the corresponding mean change in DRSP score is shown in Table 13.

Table 13. Minimum Clinically Important Difference in DRSP Score: Descriptive Statistics

Late Luteal Efficacy Period	All Subjects			Excluding Subjects With Inconsistent Response		
		Mean DRSP			Mean DRSP	
	No. of Subjects	Change From Baseline	SD	No. of Subjects	Change From Baseline	SD
DRSP total score	19	29.79	18.01	17	32.28	17.24

DRSP = daily record of severity of problems; SD = standard deviation.

DRSP Impairment: Subjects with baseline values and at least 5 efficacy period days of data for each of the 3 impairment items were included in the aggregate impairment analysis. The adjusted mean change in the DRSP aggregate impairment scores are summarized by double-blind estimated cycle and compared between treatment groups in Table 14.

Table 14. DRSP Scores for Aggregate Impairment During the Late Luteal Efficacy Period: Comparisons Within and Between Groups

Treatment	Double-Blind Estimated Cycle	No. of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	41	-3.62	0.59	<.001	0.832
	2	37	-6.30	0.54	<.001	0.005
	3	34	-6.18	0.53	<.001	0.103
	4	14	-5.23	0.87	<.001	0.953
	Last on therapy	41	-5.82	0.50	<.001	0.328
Placebo	1	52	-3.46	0.50	<.001	
	2	50	-4.34	0.44	<.001	
	3	46	-5.10	0.44	<.001	
	4	20	-5.29	0.62	<.001	
	Last on therapy	52	-5.19	0.43	<.001	

p-Values based on ANCOVA model: change = site + treatment + baseline value.
ANCOVA = analysis of covariance; DRSP = daily record of severity of problems; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; SE = standard error; vs = versus.

The aggregate impairment score decreased significantly from Baseline in both treatment groups. However, only at estimated Cycle 2 was the improvement significantly greater in the LNG 90 µg/EE 20 µg than in the placebo group.

Work Limitation Questionnaire:

WLQ Index Score: The WLQ Index score was the weighted sum of the scores from the WLQ scales (Time, Physical, Mental-Interpersonal, and Output). The mean adjusted decreases from Baseline in index scores for all 5 main items on the WLQ on (estimated) Day 1 of each double-blind estimated cycle are summarized by treatment group in Table 15. After the first double-blind estimated cycle, there was significant improvement in both

treatment groups. However, only at estimated Cycle 4 and at the last on-therapy visit was the improvement greater in the LNG 90 µg/EE 20 µg group.

Table 15. WLQ Index at Day 1: Within and Between Groups Comparisons

Treatment	Double-Blind Estimated Cycle	No. of Pairs	Adjusted Change		p-Value Within Group	p-Value vs Placebo
			Mean	SE		
LNG 90 µg/EE 20 µg	1	27	-0.54	0.76	0.812	0.954
	2	23	-5.91	1.26	<.001	0.326
	3	21	-8.88	1.31	<.001	0.119
	4	18	-9.91	1.47	<.001	0.023
	Last on therapy	30	-8.28	1.03	<.001	0.031
Placebo	1	39	-0.60	0.63	0.555	
	2	34	-4.39	0.94	<.001	
	3	33	-6.24	1.01	<.001	
	4	28	-5.56	1.18	<.001	
	Last on therapy	40	-5.32	0.89	<.001	

p-Values based on ANCOVA model: change = site + treatment + baseline value.
ANCOVA = analysis of covariance; EE = ethinyl estradiol; LNG = levonorgestrel; No. = number; SE = standard error; WLQ = Work Limitations Questionnaire; vs = versus.

Clinical Global Impression Score - Severity of Illness: The categorical analyses for all 7 categories of CGI-S responses are shown in Table 16. There were no statistical differences in the percentage of subjects with changes in any of the 4 combined categories between LNG 90 µg/EE 20 µg and placebo at any time point.

Table 16. Clinical Global Impression Score of Severity of Illness: Categorical Analysis Between Group Comparisons

Treatment	Pill Pack		CGI-S Scores														p-Value vs Placebo
			Normal		Borderline Ill		Mildly Ill		Moderately Ill		Markedly Ill		Severely Ill		Extremely Ill		
		N	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
LNG 90 µg/EE 20 µg	1	27	2	7.41	8	29.63	8	29.63	5	18.52	4	14.81	0	0.00	0	0.00	0.449
	2	26	6	23.08	8	30.77	7	26.92	3	11.54	2	7.69	0	0.00	0	0.00	0.423
	3	23	11	47.83	3	13.04	6	26.09	3	13.04	0	0.00	0	0.00	0	0.00	0.193
	4	21	11	52.38	7	33.33	1	4.76	2	9.52	0	0.00	0	0.00	0	0.00	0.363
	Last on therapy	30	13	43.33	8	26.67	5	16.67	3	10.00	1	3.33	0	0.00	0	0.00	0.456
Placebo	1	33	2	6.06	6	18.18	11	33.33	7	21.21	7	21.21	0	0.00	0	0.00	
	2	33	5	15.15	7	21.21	13	39.39	3	9.09	4	12.12	1	3.03	0	0.00	
	3	29	2	6.90	14	48.28	6	20.69	5	17.24	1	3.45	1	3.45	0	0.00	
	4	29	7	24.14	15	51.72	3	10.34	2	6.90	1	3.45	1	3.45	0	0.00	
	Last on therapy	36	7	19.44	18	50.00	5	13.89	3	8.33	2	5.56	1	2.78	0	0.00	

For the purpose of analysis, the responses were combined into 4 categories:
(Normal + Borderline + Mildly), (Moderately), (Markedly) and (Severely + Extremely).
p-Value obtained from Cochran-Mantel-Haenszel test with row mean scores.
CGI-S = Clinical Global Impression Score of Severity of Illness; EE = ethinyl estradiol; LNG = levonorgestrel; N = number of subjects; n = number of subjects with specified criteria; SE = standard error; vs = versus.

Subject Global Evaluation Scores: The categorical analysis and frequency distribution of the responses to the SGE are shown in Table 17. The differences in the distribution of responses between LNG 90 µg/EE 20 µg and placebo were significant at double-blind pill packs 2, 3, and 4.

Table 17. Subject Global Evaluation Analysis: Comparisons Between Groups

Treatment	Pill Pack	N	Subject Global Evaluation Scores														p-Value vs Placebo
			Markedly Better		Moderately Better		Slightly Better		Unchanged		Slightly Worse		Moderately Worse		Markedly Worse		
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	
LNG 90 µg/EE 20 µg	1	38	5	13.16	9	23.68	12	31.58	11	28.95	0	0.00	0	0.00	1	2.63	0.737
	2	36	9	25.00	12	33.33	11	30.56	4	11.11	0	0.00	0	0.00	0	0.00	0.042
	3	30	13	43.33	9	30.00	5	16.67	2	6.67	0	0.00	1	3.33	0	0.00	0.012
	4	28	12	42.86	11	39.29	4	14.29	0	0.00	1	3.57	0	0.00	0	0.00	0.008
	Last on therapy	43	14	32.56	15	34.88	8	18.60	4	9.30	1	2.33	1	2.33	0	0.00	0.109
Placebo	1	47	6	12.77	8	17.02	16	34.04	15	31.91	2	4.26	0	0.00	0	0.00	
	2	48	11	22.92	6	12.50	16	33.33	13	27.08	0	0.00	2	4.17	0	0.00	
	3	43	13	30.23	3	6.98	10	23.26	13	30.23	2	4.65	2	4.65	0	0.00	
	4	44	13	29.55	9	20.45	5	11.36	16	36.36	0	0.00	1	2.27	0	0.00	
	Last on therapy	52	15	28.85	10	19.23	8	15.38	18	34.62	0	0.00	1	1.92	0	0.00	

p-Value obtained from Cochran-Mantel-Haenszel test with row mean scores.
EE = ethinyl estradiol; LNG = levonorgestrel; N = number of subjects; n = number of subjects with specified criteria; vs = versus.

Safety Results:

During the double-blind treatment interval, 1 or more AEs were reported by 26 (56.5%) subjects who took LNG 90 µg/EE 20 µg and by 32 (59.3%) subjects who took placebo. In both the LNG 90 µg/EE 20 µg and placebo groups, headache (28.3% and 42.6%, respectively) was the most frequently reported event.

Serious Adverse Events (SAEs): In 1 subject who inadvertently took placebo, there was an unexpected pregnancy (characterized as an SAE) that was not considered related to study drug.

Adverse Events: During the double-blind treatment phase, treatment-emergent AEs (TEAEs) reported by at least 5% of subjects in either treatment group are summarized by body system and preferred term in Table 18. TEAEs with onset during double-blind treatment were reported by 26 (56.5%) subjects who took LNG 90 µg/EE 20 µg and by 28 (51.9%) subjects who took placebo (p=0.690).

In both the LNG 90 µg/EE 20 µg and placebo groups, headache (15.2% and 27.8%, respectively) was the most frequently reported event. None of these TEAEs occurred significantly more frequently in LNG 90 µg/EE 20 µg subjects than in placebo subjects.

Table 18. Number (%) of Subjects With Treatment-Emergent Adverse Events During the Double-Blind Treatment Phase (Reported by ≥5% of Subjects)

Body System Adverse Event	Overall p-Value	Treatment	
		LNG 90 µg/EE 20 µg	Placebo
		n=46	n=54
Any Adverse Event	0.690	26 (56.5)	28 (51.9)
Body as a whole			
Abdominal pain	0.659	3 (6.5)	2 (3.7)
Back pain	0.243	5 (10.9)	2 (3.7)
Headache	0.152	7 (15.2)	15 (27.8)
Digestive system			
Nausea	0.659	3 (6.5)	2 (3.7)
Skin and appendages			
Acne	0.122	0	4 (7.4)
Adverse event associated with miscellaneous factors			
Allergic reaction other than drug	0.247	0	3 (5.6)

Overall p-value: Fisher exact test p-value (2-tail).
Non-SAEs and SAEs are not separated out.
EE = ethinyl estradiol; LNG = levonorgestrel; SAE = serious adverse event; n = number of subject in each treatment group.

Treatment-Related Adverse Events: Two (2) subjects reported metrorrhagia that was mild in severity and considered related to study drug (p=0.209) and 1 subject reported menorrhagia that was moderate in severity and considered related to study drug (p=0.460), migraine was reported by 2 LNG 90 µg/EE 20 µg subjects and 1 placebo subject (between-group p=0.593). Treatment-related AEs are presented in Table 19.

Table 19. Number (%) of Subjects Reporting Double-blind Treatment-Related Adverse Events

Body System[a] Adverse Event	Treatment	
	LNG 90 µg/EE 20 µg	Placebo
	n=46	n=54
Any Adverse Event	11 (23.9)	9 (16.7)
Body as a whole	5 (10.9)	5 (9.3)
Abdominal pain	0	1 (1.9)
Headache	5 (10.9)	6 (11.1)
Cardiovascular system	3 (6.5)	1 (1.9)
Migraine	1 (2.2)	1 (1.9)
Digestive system	3 (6.5)	1 (1.9)
Abdominal distension	1 (2.2)	0
Increased appetite	1 (2.2)	0
Nausea	2 (4.3)	1 (1.9)
Nervous system	3 (6.5)	1 (1.9)
Emotional lability	2 (4.3)	0
Hostility	1 (2.2)	0
Insomnia	0	1 (1.9)
Skin and appendages	1 (2.2)	2 (3.7)
Acne	0	2 (3.7)
Seborrhea	1 (2.2)	0
Urogenital system	5 (10.9)	0
Breast pain	2 (4.3)	0
Dysmenorrhea	1 (2.2)	0
Menorrhagia	1 (2.2)	0
Metrorrhagia	2 (4.3)	0
Term not classifiable	1 (2.2)	0
Reaction unevaluable	1 (2.2)	0

EE = ethinyl estradiol; LNG = levonorgestrel; n = number of subjects with specific adverse events.
a. Body system total were not necessarily the sum of the individual adverse events since a subject may report ≥2 different adverse event in the same body system.

Discontinuations: AEs were reported as the primary reason for discontinuation of study drug by 4 (8.7 %) LNG 90 µg/EE 20 µg subjects and 0 placebo subjects (p=0.042). The 4 AEs for which LNG 90 µg/EE 20 µg subjects discontinued study medication were palpitation, emotional lability, abdominal distension, and migraine.

Death: No deaths occurred in the study.

Laboratory Evaluations: The baseline mean fasting blood glucose, total, high density lipoprotein and low density lipoprotein cholesterol, and triglyceride concentrations were similar between groups.

The baseline mean levels of total and direct bilirubin, alkaline phosphatase, aspartate amino transferase, and alanine amino transferase were similar between groups. There were no significant differences between groups in any of the liver function tests at pill-pack-4 except for alkaline phosphatase.

The mean hemoglobin and hematocrit values were similar between groups at Baseline and there were no significant differences in mean change from Baseline between groups.

Vital sign measurements recorded at Baseline were compared with results recorded at the posttreatment evaluation. There were no statistically significant changes over time in vital sign measurements or body weight during the course of this study.

CONCLUSIONS:

The primary objective of this study was to compare the effect of treatment with LNG 90 µg/EE 20 µg administered in a continuous daily regimen with that of placebo in women 18 to 49 years of age who met DSM-IV criteria for PMDD.

The primary efficacy measures, mean DRSP 21-item total daily scores during the late luteal phase and during the worst 5 days, decreased significantly from Baseline in both groups during the first double-blind estimated cycle and at the last on-therapy efficacy period. However, only during double-blind Cycles 2 and 3 were the mean decreases in the DRSP total score significantly greater in the LNG 90 µg/EE 20 µg group than in the placebo group. The inclusion of more subjects in the sensitivity analyses did not appreciably alter the findings.

Although treatment with LNG 90 µg/EE 20 µg produced a greater response in primary and secondary efficacy variables than did placebo, the placebo effect on these measurements was likewise greater than anticipated, and did not allow for consistent significant differences between groups.

In summary, a larger than anticipated placebo response was observed that resulted in inconsistent treatment effects on measures of PMDD between LNG 90 µg/EE 20 µg and placebo.

This study shows that, continuous-use LNG 90 µg/EE 20 µg has a safety profile comparable with placebo and consistent with that of a 21-day cyclic low-dose oral contraceptive containing LNG 100 µg/EE 20 µg. These results confirm the findings of larger Phase 3 trials of 2457 subjects taking LNG 90 µg/EE 20 µg for up to 1 year.