CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA/Serial Number:	21-873 (Class 1 Resubmission)
Drug Name:	YAZ (Drospirenone 3 mg/ethinylestradiol 0.02 mg tablets)
Indication(s):	Premenopausal dysphoric disorder (PMDD)
Applicant:	Berlex Laboratories, Inc.
Date(s):	
Submission:	March 01, 2006
User Fee Goal:	September 01, 2006
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Shahla S. Farr, M.S.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products
Clinical Team:	Lisa Soule, M.D. - Scot Monroe, M.D.
Project Manager:	Charlene Williamson

Background:

NDA 21-873 was originally submitted on 12-22-04 for the indication of premenopausal dysphoric disorder (PMDD). Moreover, the Sponsor had presented the same drug product under NDA 21-676 for indication of contraception on October 16, 2003. Both NDAs were deemed acceptable from a statistical perspective.

Purpose:

The purpose of the March 01, 2006 submission of NDA 21-873 for the indication of (PMDD) was, solely, for safety issues and concerns of the Medical Division.

Action:

No new statistical evaluation was requested for this submission. Hence, from a statistical standpoint **no further action is indicated (NAI)**.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-676 (cross referenced with NDA 21-873)

Drug Name: YAZ (Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg) Tablets

Indication(s): Prevent Pregnancy (Oral Contraception)

Applicant: Berlex Laboratories, Inc.

Date(s):

Submission: Complete Response: June 16, 2005

User Fee Goal: March 16, 2006 (Extended)

Review Priority: Standard

Biometrics Division: DOB2

Statistical Reviewer: Shahla S. Farr, M. s.

Concurring Reviewers: Mike Welch, Ph.D. – Ed Nevius, Ph.D.

Medical Division: Division of Reproductive and Urological Drug Products (DRUDP) HFD-580

Clinical Team:

Medical Officer: Gerald Willett, M.D.

Medical Team Leader: Scott Monroe, M.D.

Project Manager: Charlene Williamson

1. EXECUTIVE SUMMARY

Originally, the Sponsor had submitted NDA 21-676 for YAZ Tablets, in a 24-day regimen for the indication of oral contraception. Consequently, the Sponsor received an approvable letter from the Agency. In response to the approvable letter and the request from the Agency, Berlex submitted a study for Follicular Inhibition or Ovulation Inhibition (Protocol # 308382). Therefore, the focus of this review is on the above mentioned Study.

1.1 Conclusions
There were several issues and problems with this study; such as no set hypothesis prior the study initiation, no statistical rational for the sample size or for the statistical methodology, the low sample size of 100, and a short duration of only 3 cycles. Nevertheless, there is an apparent trend that the 24-day treatment might have some benefit over the 21-day. The statistical methodology that the sponsor has used is reasonable; however the study results can only be considered descriptive and not confirmatory. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.

Comparison of the results of the recalculations of the primary efficacy endpoints with the original evaluation, show a trend toward better follicular suppression obtained with the 24 day regimen compared to the 21 day regimen.

1.2 Brief Overview of the Clinical Study
This was a single center, double-blind, randomized study to compare the effect of SH T 00186 D on follicular development (follicular size and the incidence of ovulation in normal cycles) in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3.

1.3 Statistical Issues and Findings
There were several issues and problems with this study; such as no set hypothesis prior the study initiation, no statistical rational for the sample size or for the statistical methodology, the low sample size of 100, a short duration of only 3 cycles. Thus results can only be considered to be descriptive. The 24-day treatment shows a trend that would indicate some benefit over the 21-day treatment.

2. INTRODUCTION

2.1 Overview
Originally, the Sponsor had submitted NDA 21-676 for YAZ Tablets, in a 24-day regimen for the indication of oral contraception. Consequently, the Sponsor received an approvable letter from the Agency. In response to the approvable letter and the request from the Agency, Berlex submitted a study for Follicular Inhibition or Ovulation Inhibition (Protocol # 308382). Therefore, the focus of this review is on the above mentioned Study.

The original NDA 21-676 was submitted on October 16, 2003 for YAZ Tablets, in a 24-day regimen, for the indication of oral contraception. Berlex received an approvable letter for this NDA on November 17, 2004, during the first review cycle., Berlex responded to the approvable letter with a resubmission dated June 16, 2005.

Reference is also made to NDA 21-873 submitted on December 22, 2004 for YAZ Tablets as an oral contraceptive (OC) and for the treatment of symptoms of premenstrual dysphoric disorder. On July 25, the Sponsor submitted the follicular inhibition study to NDA 21-873 by way of cross reference to NDA 21-676.

On October 21, 2005, the Division sent Berlex a clinical information request with comments regarding Protocol 308382. The final report for this ovulation inhibition study, Report A25848, was included in the resubmission to NDA 21-676. The clinical information request was the recalculation of the primary efficacy endpoints for the two treatment groups excluding the subjects with no progesterone level of 5ng/mL or greater during the ovulation assessment period.

3.   STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This was a single center, double-blind, randomized study to compare the effect of SH T 00186 D on follicular development (follicular size and the incidence of ovulation in normal cycles) in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3.

Previously (**May 5th**) , the Sponsor had submitted data based on 99 subjects; out of which 50 were treated with the 21-day regimen and 49 were the 24-day regimen users. In that submission, Hoogland scores in cycles 2 and 3 were analyzed using a proportional odds model and an odds ratio between treatments.

May 5th (Based on 99 Subjects)
Estimated odds ratio for having a lower Hoogland score by cycle - FAS , PPS

Cycle	Analysis sets	Estimated odds ratio	95% CI
2	FAS	6.91	[2.67; 20.49]
	PPS	6.01	[2.29; 17.94]
3	FAS and PPS	3.06	[1.44; 6.65]

In response to the Division's October 21, 2005 request, additional analysis was performed and submitted by the Sponsor. The evaluation of the primary efficacy variables was redone, excluding 21 subjects (11 subjects from the 24-day regimen and 10 subjects from the 21-day regimen) specified by the FDA.

Odds ratios for treatment effect in cycles 2 and 3 - **FAS excluding the 21 subjects** specified by the FDA:

Cycle	Estimated Odds ratio	95% CI
2	7.65	[2.82 ; 23.57]
3*	2.35	[1.03 ; 5.47]

* The results of the cycle 3 were the same for FAS as well as PPS

Based on another request from the Division to exclude subjects with progesterone levels not higher than 1.57 ng/ml in the baseline cycle, the evaluation of the primary efficacy variables was repeated.

Odds ratios for treatment effect in cycles 2 and 3 – **PPS excluding the 8 subjects** with all baseline progesterone levels below 1.57 ng/ml:

Cycle	Odds ratio	95% CI
2	6.55	[2.46 ; 19.78]
3*	2.68	[1.24 ; 5.92]

* The results of the cycle 3 were the same for FAS as well as PPS

Odds ratios for treatment effect in cycles 2 and 3 - **FAS excluding the 8 subjects** with all baseline progesterone levels below 1.57 ng/ml:

Cycle	Odds ratio	95% CI
2	7.56	[2.88 ; 22.68]
3	2.68	[1.24 ; 5.92]

4.   CONCLUSIONS

This study lacked a prospective statistical analysis plan and can only be considered to be descriptive. There is an apparent trend that the 24-day regimen might have some benefit over the 21-day regimen. The statistical methods that the sponsor has used seems to be reasonable. This reviewer assessed and re-evaluated the sponsors' results. The findings were similar to that of the Sponsor's.

Comparing the results of three different recalculations of the primary efficacy endpoints with the original evaluation, better follicular suppression is indicated with the 24 day regimen compared to the 21 day regimen.

/s/

Mike Welch
1/20/2006 10:53:25 AM
BIOMETRICS
Submitted for Shahla Farr. Concur with review. This review
is cross-referenced to NDA 21676

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-873

Drug Name: YAZ (Drospirenone 3mg/Ethinyl Estradiol 0.020 mg) Tablets

Indication(s): Oral Contraceptive (OC) & Premenstrual Dysphoric Disorder (PMDD)

Applicant: Berlex Labs

Date(s):

  Submission   December 23, 2004

  User Fee Goal   January 23, 2006 (extended)

Review Priority: Standard

Biometrics Division: Division of Biometrics 2

Statistical Reviewer: Shahla S. Farr, M.S.

Concurring Reviewers: Mike Welch, Ph.D. , Ed Nevius, Ph.D.

Medical Division: Division of Reproductive and Urologic Products

Clinical Team: Lisa Soule, M.D. , Medical Reviewer - Scott Monroe, M.D., Team Leader

Project Manager: Charlene Williamson

Keywords:

NDA Review, Clinical Trials, Cross-Over Study

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor has submitted this efficacy supplement for drospirenone 3 mg and ethinyl estradiol 20 ug (DRSP/EE) Tablets in a 24-day regimen for 3 menstrual cycle-treatment period to serve as the support of their secondary indications of Premenstrual Dysphoric Disorder (PMDD) for women desiring birth control. The sponsor had, previously, submitted another clinical trial data under NDA # 21-676 for their primary indication of prevention of pregnancy by an Oral Contraception (OC) which was reviewed separately.

This new submission contains two studies that provide relevant efficacy data and, therefore, will be the focus of this review: Study A21566 and Study A07545. The primary efficacy variable for both of these studies is the Daily Record of Severity of Problems (DRSP) scale. The primary efficacy endpoint was assessed based on the difference in DRSP scores between baseline and the average over 3 treatment cycles.

The results supporting the primary indication of OC were described in the NDA # 21-676. Therefore, this submission only concentrates on the secondary indication of PMDD.

1.1 Conclusions

Study A21566, the placebo controlled, parallel group trial, for the indication Premenstrual Dysphoric Disorder (PMDD) showed statistically significant superiority ($p < 0.001$) based on the results submitted by the sponsor. Based on the analysis of the reviewer, using electronic data submitted to the Agency, the results were consistent with those of the sponsor.

Study A07545, the cross-over study also showed statistically significant results in both the sponsor's results as well as the reviewer's ($p \leq 0.05$).

Based on the reviewer's analyses of the data provided by the sponsor, in electronic format, the reviewer's findings are in agreement with that of the sponsor's.

1.2 Brief Overview of Clinical Studies

The sponsor has provided two studies that present efficacy data for the indication of PMDD. Study A21566 and Study A07545. Study A21566 is a multi-center, randomized, double-blind, and parallel design comparing DRSP/EE vs. Placebo. A total of 449 women participated in this study.

Study A07545 was designed and conducted as a multi-center, randomized, double-blind, and cross-over trial. A total of 64 women were randomized to receive both DRSP/EE and Placebo. Because of difficulties recruiting volunteers, this study was pre-maturely stopped. The primary efficacy variable for both of these studies is the Daily Record of Severity of Problems (DRSP) scale.

1.3 Statistical Issues and Findings

The primary efficacy endpoint was assessed based on the change in DRSP scores between baseline and the average over 3 treatment cycles. The DRSP score was calculated by first taking the average of each of the first 21 items of the DRSP scale individually over the last 5 days before menses and then taking the sum of these first 21 items averages. A decrease in scores indicates improvement in symptoms. Hypothesis testing was done based on 2-sided tests and at the 0.05 level of significance. The primary efficacy variable was analyzed with a weighted ANCOVA model containing treatment and centers as factors, and baseline as a covariate.

2. INTRODUCTION

2.1 Overview

The sponsor has submitted this efficacy supplement for drospirenone 3 mg and ethinyl estradiol 20 ug (DRSP/EE) Tablets in a 24-day regimen for 3 menstrual cycle-treatment period to serve as the support of their secondary indications of Premenstrual Dysphoric Disorder (PMDD) for women desiring birth control. The sponsor had, previously, submitted other clinical data under NDA # 21-676 for their primary indication of prevention of pregnancy by an Oral Contraception (OC) which was reviewed separately.

This new submission contains one study that provides relevant efficacy data and, therefore, will be the focus of this review; Study A21566. The Sponsor had planned one other study, a cross-over trial (Study A07545). However, enrollment for this trial was terminated prematurely. Hence, the number of subjects in this cross-over trial did not reach the sample size planned previously. Nonetheless, the results of this study were submitted to the agency.

The primary efficacy variable for both of these studies is the Daily Record of Severity of Problems (DRSP) scale. The primary efficacy endpoint was assessed based on the difference in DRSP scores between baseline and the average over 3 treatment cycles.

The results supporting the primary indication of OC were described in the NDA #.21-676. Therefore, this submission only concentrates on the secondary indication of PMDD.

Table 1 provides a brief summary of the two pivotal studies under this review.

Table 1: Brief Summary of the Two Pivotal Studies

Report/Protocol #	Study Type (Phase)	Study Design Duration (Regimen)	Treatment (N Treated)	Age Range (Mean)
A21566/304049	Efficacy/Safety (Phase 3)	Multi-center, randomized, double blind, placebo-controlled, **Parallel** 3 Cycles (24-Day)	DRSP/EE (231)	18-40 (31.0)
			Placebo (218)	18-42 (32.0)
A07545/305141	Efficacy/Safety (Phase 3)	Multi-center, randomized, double blind, placebo-controlled, **Crossover** 6 Cycles (24-Day)	DRSP/EE; Placebo [a] (34)	19-39 (31.0)
			Placebo; DRSP/EE [b] (30)	20-40 (33.0)

DRSP = drospirenone; EE = ethinyl estradiol; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg.
a Treatment group first received DRSP/EE for 3 treatment cycles, then no study medication for 1 cycle, and then placebo for 3 treatment cycles.
b Treatment group first received placebo for 3 treatment cycles, then no study medication for 1 cycle, and then DRSP/EE for 3 treatment cycles.

The studies consisted of 2 phases: 1) The qualification phase consisting of 2 run-in (menstrual) cycles, and 2) The treatment phase consisting of 3 treatment cycles with DRSP/EE or placebo.

The Primary Objective

The objectives of the two studies were to evaluate the efficacy and safety of drospirenone 3 mg/ ethinyl estradiol 20 μg (DRSP/EE) compared to placebo in treating the symptoms of PMDD. In other words, to test the null hypothesis that the expected Daily Record of Severity of Problems (DRSP) scale for the DRSP/EE Tablets is equal to that for the placebo group against the alternative hypothesis that they not equal.

4

2.2 Data Sources

This submission was provided in electronic format: \\CDSESUB1\N21873\N_000\2004-12-22. The sponsor had provided the SAS data for both Studies A21566 and A07545 at the time of NDA submission. Due to a corrupted disk that contained information for Study A21566, the sponsor submitted another CD for the above study later in May, 2005 under: \\CDSESUB1\N21873\N_000\2005-05-20.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Primary efficacy variable

The primary efficacy endpoint, for both of the studies, was the Daily Record of Severity of Problems (DRSP) scale that is a validated disease-specific questionnaire used to document daily symptom severity in Pre-Menstrual Dysphoric Disorder (PMDD). The first 21 items are divided into 2 categories: physical and nonphysical or "mood items". Subjects completed this questionnaire each evening during the study, starting on the first day of their menses during Run-in Cycle 1. The subjects rated the degree to which they experienced each of the symptoms on a scale of 1 (not at all) to 6 (extreme).

This variable was assessed based on the difference in the DRSP scores between baseline and the average over 3 treatment cycles. This endpoint had been agreed upon between Berlex and the Division of Neuropharmacological Drug Products (DNDP) in a meeting on 23 Jan 2001.

In order to calculate the DRSP score for each cycle, the Sponsor averaged the first 21 DRSP items over the last 5 days before menses and then the averages for each of the first 21 items were summed. The primary efficacy variable was the difference of the average of the DRSP treatment cycle scores and the baseline DRSP scores. A decrease in scores indicated improvement in symptoms.

In this review, first the average for each DRSP item individually (D1, D2... D21) over all non-missing subjects was summed for the two run-in periods (the baseline cycles). Then the same procedure was followed to assess the averages for the three treatment cycles. Finally, the averages of the baseline DRSP scores were subtracted from the mean of the DRSP scores for the treatment period for each DRSP item individually. A decrease in scores indicates improvement in symptoms.

The Sponsor's primary efficacy analyses were based on the full analysis set, Intent-to-Treat (ITT) defined as all randomized subjects who took at least one dose of study medication.

Secondary efficacy variables
- Three functional impairment items in DRSP:
    1. Productivity at work, home or school
    2. Interference with hobbies or social activities and
    3. Interference with relationship
- CGI (Clinical Global Improvement)
- SF-36 (Health Survey)
- Endicott Q-LES-Q (Quality of Life Enjoyment and Satisfaction Questionnaire) (short version)
- PMTS Scale (Premenstrual Tension Syndrome Scale)

5

Data Sets Analyzed

The Sponsor had considered two analysis sets for the efficacy evaluation: the full analysis set and the per protocol set. The full analysis set included all subjects who were randomized to study medication and were known to have taken at least 1 dose of study medication. A subject was included in the per-protocol set if she was included in the full analysis set, did not take any prohibited medication, had 75% or higher study drug compliance, had no violations of the inclusion/exclusion criteria, provided a measurement of the DRSP score for at least 1 treatment cycle, and had no major protocol violations. These were not the definitions that were in the protocol; however they were in the Statistical Analysis Plan that was submitted to the Division for review on 06 May 2004 prior to database lock. In this review, all subjects with any available efficacy data have been included in the analyses of efficacy.

Analysis Methods

In both studies, the Sponsor compared the primary efficacy variable, derived from the sum of the first 21 items of the DRSP, between treatment groups with a weighted analysis of covariance (ANCOVA) model that included treatment and center as factors, and baseline as a covariate. First, the baseline value was calculated for each subject as the average of the 2 run-in cycles score. Then the change from baseline at each treatment cycle was calculated. The average of the changes from baseline at the treatment cycles were to be analyzed under the assumption that this measurement is normally distributed. The analysis model included the treatment group and center as factors and baseline as a covariate. The number of non-missing treatment cycle DRSP scores (between 1 and 3 per subject) was used as the weight. The assumption of homogeneity of the slopes in the ANCOVA model was tested and if this assumption was violated at the 0.05 level of significance, the covariate was dropped from the model. The normality assumption on the average of the changes from baseline was verified by the residual analysis. If the residual analysis does not support the normality assumption, the ranks of the original data was to be analyzed using a two-way ANOVA. The rank ANOVA model would only include the treatment group and center as factors.

Study # A21566

Randomization

Subjects were assigned a 6-digit screening number, which was used as their identification number for the duration of the study. Subjects eligible for the treatment phase were assigned a 6-digit randomization number based on permuted block randomization at visit 4. Each subject's screening and randomization numbers were recorded in the CRF.

Sample Size Calculation & Handling of Missing Data

Originally, the planned sample size of approximately 408 subjects was chosen to provide a 90% power with a 0.05 significance level to detect a difference of 6.5 points in the DRSP score (sum of first 21 items) between treatment and placebo under the assumptions of a between subject standard deviation of 18 points and a projected dropout rate of 20%. The anticipated dropout rate was changed to 30% in a protocol amendment, resulting in a power of 85%. However, the actual enrollment was 450 subjects (449 subjects took study medication). Figure 1 (later in this review) shows actual enrollment and drop out trend).

A total of 3497 subjects were screened for inclusion into the study; 2245 subjects entered the 2-cycle qualification phase. Of these, 1795 subjects were prematurely discontinued from the qualification phase. A total of 450 subjects were randomized of which, a total of 232 subjects were randomized to DRSP/EE and 218 subjects were randomized to treatment with placebo. One subject in the DRSP/EE treatment group never took any drug. A total of 161 (69.4%) of the 232 subjects in the DRSP/EE treatment group, and 167 (76.6%) of the 218 subjects in the placebo treatment group completed the study. Seventy-one

6

(30.6%) subjects in the DRSP/EE treatment group and 51 (23.4%) subjects in the placebo treatment group prematurely discontinued from the study. Table 2, later in this review, explains the reasons for discontinuation of the subjects.

If a DRSP item was missing for a day during the last 5 days before menses, the missing item for that day was imputed by averaging the 2 non-missing data of the days bordering the missing value. However, if a DRSP item was missing 1 day or 5 days prior to menses, it could not be imputed. Furthermore, if 2 consecutive days had a missing value, neither could be imputed. Upon handling the missing data as just described, if more than 2 days of a DRSP item were still missing, the average for that DRSP item was set as missing. If the average of any of the 21 DRSP items was missing, then the DRSP score was set as missing.

Pooling of Study Centers
In the protocol, the Sponsor had planned to pool the sites with small number of subjects. Seventy seven investigators in the United States screened subjects for inclusion into the study. In the Sponsor's analyses, centers with at least 5 per-protocol subjects were pooled and assigned a pooled center number and were not pooled with other centers. The pooled centers were then used for the analysis of all variables. In this review, for the analysis purposes, centers with a total of eight subjects or less were pooled in a manner to achieve a reasonable number of subjects (between 10 and 15) in each center. Hence, the number of sites was reduced from 64 to a total of 29, ranging from 9 to 40 subjects in each center.

Subjects with Protocol Deviations & Patient Disposition
A total of 195 (84%) of the 231 subjects in the DRSP/EE treatment group and 177 (81%) of the 218 subjects in the placebo treatment group had at least one protocol deviation. A total of 53 (23%) subjects in the DRSP/EE treatment group and 42 (19%) subjects in the placebo arm had at least one protocol deviation that was considered major, as shown in Table 2. These 95 subjects were excluded from the per protocol analysis set.

Table 2: Sponsor's Data - Study A21566
Number (%) of Subjects with Major Protocol Deviations

	Treatment Group	
	DRSP/EE N=231	Placebo N=218
Number of subjects with any major deviation	53 (22.94%)	42 (19.27%)
Inclusion/exclusion error at study entry	37 (16.02%)	29 (13.30%)
Randomization/registration error	1 (0.43%)	2 (0.92%)
Excluded concomitant treatment	5 (2.16%)	5 (2.29%)
Treatment deviation [a]	22 (9.52%)	22 (10.09%)
Procedure deviation	1 (0.43%)[b]	0 (0.00%)

Note: The safety analysis was based on the full analysis set.
a Deviations included < 75% compliant, took 2 or more pills for 3 or more consecutive days, and took 3 or more tablets in 1 day.
b Subject 860015 did not have confirmation of diary entries for 9/13 to 9/16.
Subjects with multiple deviations within the same category are counted once per category.
DRSP/EE = drospirenone 3 mg/ethinyl estradiol 20 □g.
Reference: Sponsor's Table 6 and Listing 16.2.2.1, Appendix 16.2.2.

A total of 192 (83%) subjects in the DRSP/EE treatment group and 170 (78%) subjects in the placebo arm had at least one protocol deviation that was considered minor.
Improper study conduct was discovered at Site 86 for this study. In total at this site, 34 subjects were screened for the study and 3 subjects were randomized. Two subjects (860001 and 860015) completed the study and 1 subject (860007) prematurely discontinued the study due to withdrawal of consent. These subjects were contacted and were asked each to re-review their diary and sign a statement confirming that

7

all diary entries were self-recorded. Statements were received from Subjects 860007 and 860001. Subject 860015 noted that for some entries the handwriting appeared not to be hers. Her diary data were not included in the per protocol analysis. Subject 860007 did not return any treatment diaries; she was also not in the per-protocol population.

Subject Drop-Out, Demographic & Baseline Characteristics

Figure 1 displays the trend of the subject drop out throughout Study # A21566.
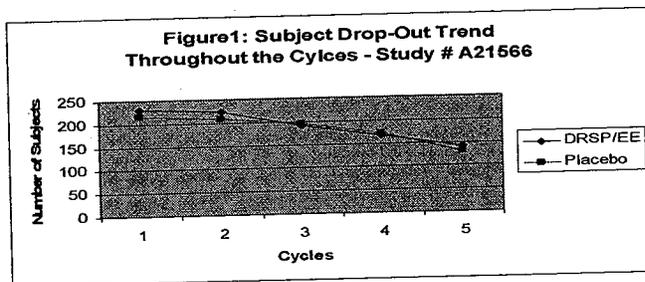
A total of 450 healthy and in the reproductive age women who had a diagnosis of PMDD were analyzed. Data was available for 448 subjects in the electronic data submitted to the Agency. The majority of the women in both treatment groups were Caucasian (176 of 231, 76.19%, in the DRSP/EE treatment group and 169 of 217, 77.88%, in the placebo treatment group). Twenty nine (12.6%) subjects in DRSP/EE and 36 (16.6%) subjects in the Placebo arm were smokers. However, this difference was not statistically significant (p<0.23). Table 3 shows the mean and standard deviation for baseline characteristics and demographics for continuous variables by treatments arm. There were no important differences noted between treatment group baseline characteristics.

Table 3: Demographics & Baseline Characteristics of Treatment Groups –Study A21566

Variable (N)	Mean ± Std. (n)	
	Treatment Arm	
	DRSP/EE	Placebo
Baseline DRSP (447)	77.6 ± 17 (231)	79 ± 18 (216)
Age (448)	31 ± 5.6 (231)	32 ± 5.5 (217)
Weight (445)	71 ± 13 (231)	68.5 ± 13 (214)
Height (445)	166 ± 6 (230)	166 ± 7 (215)
BMI (444)	26 ± 4.6 (230)	25 ± 4.3 (214)

Analysis
The Sponsor compared the primary efficacy variable between treatment groups with a weighted analysis of covariance (ANCOVA) model that included treatment and center as factors, and baseline as a covariate.

Tables 4 and 5 summarize the efficacy results achieved by the sponsor and by this reviewer, respectively.

Table 4: Sponsor's Results, Study A21566
Statistical Comparison between Treatments of Mean Change from Baseline in DRSP Scores

Efficacy Variable (N)	Mean (n)		Difference	P- Value
	DRSP/EE	Placebo		0.0001
Difference from Baseline in DRSP Scale (384)	-37.49 (190)	-29.99 (194)	-7.5	

- The primary efficacy variable was the difference from baseline of the average over 3 treatment cycles of the sum of the averages over the last 5 days before menses of the first 21 items of the DRSP scale.
- ANCOVA = analysis of covariance; DRSP = Daily Record of Severity of Problems scale;
- DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg;
- N = total number of subjects in treatment group;
- n = total number of subjects with available data.
- Mean change from baseline in the average of adjusted means of all 3 treatment cycles.
- The difference in adjusted treatment means (DRSP/EE minus placebo).
- P-value from ANCOVA with terms for treatment and center, baseline as covariate.

Table 5: Reviewer's Results, Study A21566
Statistical Comparison between Treatments of Mean Change from Baseline in DRSP Scores

Efficacy Variable (N)	Mean ± Std. (n)		Difference (95% CI)	P- Value
	Treatment Arm			
	DRSP/EE	Placebo		0.005*
Difference from Baseline in DRSP Scale (384)	-36.4 ± 20 (190)	-29.8 ± 23 (194)	-6.7 (-10, -2)	

*Proc mixed with treatment, cycle, treatment by cycle and baseline DRSP in the model.

As it is seen in the Table above, the "Difference in Mean Change" calculated by the Sponsor and that of this reviewer were different by just 0.8 (7.5 - 6.7 = 0.8). Nonetheless, the results of the analyses were similar in the end (p ≤ 0.005) and the small discrepancy does not alter the results. In addition, no center or center by treatment effect was detected in the analyis.

Table 6 along with the Figure 2 illustrates the change in DRSP Scores by cycle.

Table 6: Reviewer's Results, Study A21566
Mean ± Std. for DRSP Scores by Cycle

Cycle	Mean ± Std. (n)		
	DRSP	Placebo	Difference
Run-in 1 *	76 ± 19 (231)	78 ± 20 (216)	-2 ± 19
Run-in 2 *	79 ± 19 (223)	79 ± 20 (208)	-0.3 ± 19
TRT Cycle1	43 ± 20 (190)	51 ± 24 (195)	-8 ± 22
TRT Cycle2	40 ± 19 (166)	47 ± 23 (170)	-7 ± 21
TRT Cycle3	37 ± 17 (140)	47 ± 25 (130)	-10 ± 21

* Baseline Value is the average of both Run-in periods

9

Figure 2: Study # A21566 DRSP Scores by Cycle
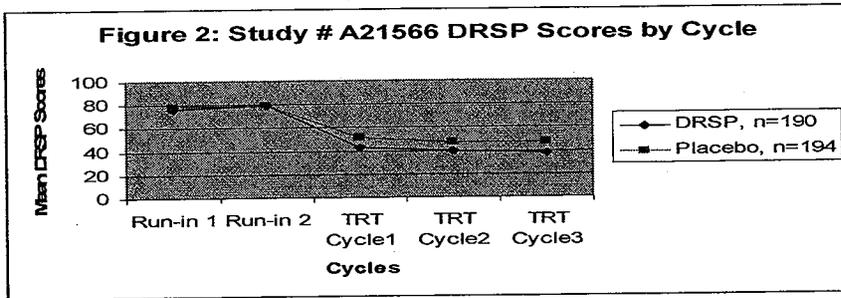
Study # A07545 (Cross-Over Study)

As mentioned previously in this review, the Sponsor had planned one cross-over trial (Study # A07545). However, enrollment for this trial was terminated prematurely. Hence, the number of subjects did not reach to the sample size planned previously. Nonetheless, the results of this study were submitted to the agency.

Study # A07545 was designed and conducted as a multi-center, randomized, double-blind, cross-over trial. A total of 64 women from 24 US centers were randomized to receive both DRSP/EE and Placebo. At the pre-NDA stage, the Division raised a concern regarding the Sponsor's pre-mature discontinuation of the Study. The sponsor clarified that the reason for early termination of the study was a slow subject-enrollment.

Determination of sample size

Originally, approximately a total of 126 subjects were planned for this study. The planned sample size of 126 subjects was chosen to provide a 90% power to detect a difference of 6.5 points in the DRSP score (sum of first 21 items) between treatment and placebo under the assumptions of a between subject standard deviation of 18 points and a correlation of 0.50 between the within subject measurements from the 2 periods, and a projected dropout rate of 30%. Because of difficulty in subject enrollment and budgetary constraints, recruitment was stopped at a sample size of 65.

Subject Drop-Out, Demographic & Baseline Characteristics

64 subjects were randomized and took study medication. A total of 34 subjects were randomized to the treatment sequence DRSP/EE, placebo and 30 subjects were randomized to the treatment sequence placebo, DRSP/EE. Fourteen subjects in the DRSP/EE, placebo treatment sequence, and 11 subjects in the placebo, DRSP/EE treatment sequence completed the study. Twenty (58.8%) of the 34 subjects in the DRSP/EE, placebo treatment sequence and 19 (63.3%) of the 30 subjects in the placebo, DRSP/EE treatment sequence prematurely discontinued from the study.

Figures 3 and 4 show the drop-out trend for periods 1 and 2 of the study, respectively.

Figure 3: Subject Drop-Out Trend
1st Period - Study # A07545

Figure 4: Subject Drop-Out Trend
2nd Period - Study # A07545
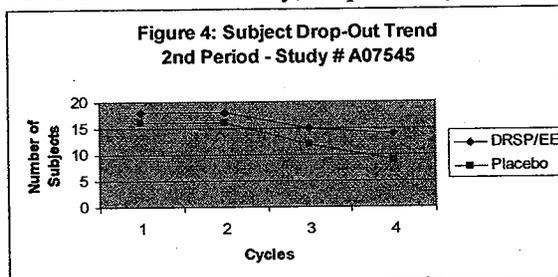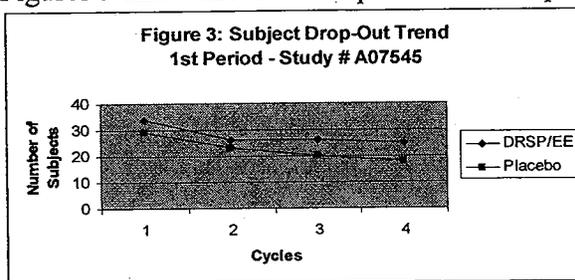
A total of 63 healthy and in the reproductive age women who had a diagnosis of PMDD were analyzed. The majority of the women in both treatment sequences were Caucasian (23 of 34, 68%, in the DRSP/EE, placebo sequence and 24 of 29, 83%, in the placebo, DRSP/EE sequence).

Table 7 displays the mean and standard deviation for baseline characteristics and demographics for continuous variables by treatments arms.

Table 7: Demographics & Baseline Characteristics of Treatment Groups Study A07545, Cross Over Study

Variable (N)	Mean ± Std. (n)			
	Treatment Arm			
	DRSP/EE		Placebo	
Baseline DRSP, Period 1 (63)	74 ± 18	(34)	71 ± 16	(29)
Baseline DRSP, Period 2 (34)	40 ± 14	(18)	57 ± 23	(16)
Age (63)	32 ± 5	(34)	32 ± 6	(29)
Weight (63)	69 ± 16	(34)	74 ± 13	(29)
Height (63)	162 ± 6	(34)	166 ± 7	(29)
BMI (49)	26 ± 5	(34)	27 ± 5	(29)

A statistically significant difference was observed between the two treatment groups for the baseline sum of DRSP in the second period (p=0.03). This could be an indication that the wash-out period was not sufficient to reduce or eliminate the drug carry-over effect. No other statistically significant differences were found in the demographics and baseline characteristics between the treatment groups.

Analysis

Tables 8 and 9 show the Sponsor's and the reviewers' results for the descriptive statistics for change from baseline in DRSP treatment period scores (first 21 items) by treatment sequence, respectively.

Table 8: Sponsor's Results, Study # A07545
Descriptive Statistics for Change from Baseline in DRSP Treatment Period Scores (First 21 Items) by Treatment Sequence (Full Analysis Set)

		Treatment	
		DRSP/EE N = 34	Placebo N = 30
Treatment Period [a]			
Treatment period 1	n	26	23
	Mean ±SD	-33.96 ±18.267	-19.95 ±20.840
Treatment period 2	n	16	18
	Mean ±SD	-17.04 ±15.379	7.50 ±16.227

a Treatment period 1 score is the average of the change from baseline in DRSP cycle scores from treatment cycles 1 to 3; treatment period 2 score is the average of the change from baseline in DRSP cycle scores from treatment cycles 4 to 6.
DRSP/EE = drospirenone 3 mg/ethinyl estradiol 20 □g; DRSP score = Daily Record of Severity of Problems score; SD = standard deviation.
Reference: Sponsor's Table 14.

Table 9: Reviewer's Results, Study # A07545
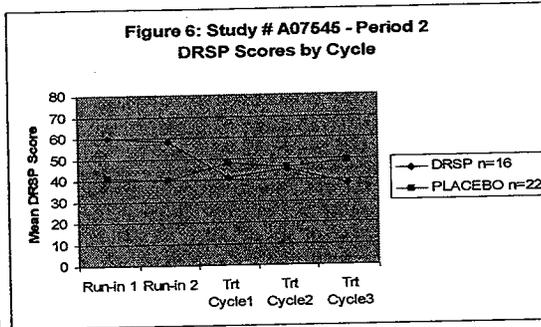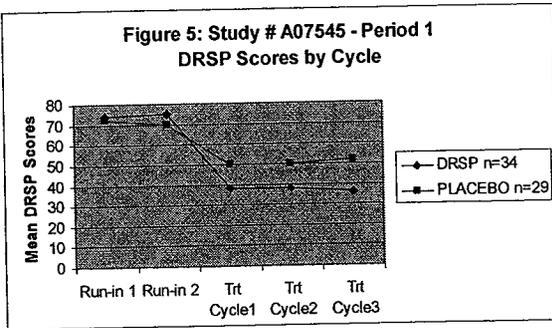**Statistical Comparison between Treatments for Mean Change from Baseline in DRSP Scores**

Primary Efficacy Variable	Mean ± Std. (n)		Difference (95% CI)	P- Value
	Treatment Arm			
	DRSP/EE	Placebo		
Difference from Baseline in DRSP Scale Period 1 (n=49)	-34 ± 18 (26)	-20 ± 21 (23)	-14 (-25, -3)	0.02
Difference from Baseline in DRSP Scale Period 2 (n=34)	-17 ± 15 (16)	+7.5 ± 16 (18)	-24.5 (-36, -13)	0.001

As it can be observed, the results for change from baseline in DRSP score by period are similar between the sponsor's and the reviewer's analysis. When the two arms were compared, statistically significant results were observed for the first period in the mean change from baseline is DRSP scores ($p \leq 0.02$). For second period, however, it should be noted that the Placebo group (subjects who were in the active treatment in the first period) started the second period of the treatment with a smaller DRSP score. Period 2 baseline value for DRSP group was 58 vs. 40 for the Placebo group. The drop-out rate, possible carry over effect and inability to maintain the randomization (due to drop-outs) were all problems for second period of the cross-over study. Nonetheless, strong results still held for the second period (p=0.001).

Table 10 and Figures 5 and 6 illustrate the pattern of change is the actual DRSP Scores through out the cycles, by each period.

Table 10: Reviewer's Results, Study #A07545
Mean ± Std. for DRSP Scores by Cycle

Cycle	Mean ± Std. (n)		
Period 1	DRSP	Placebo	Difference
Run-in 1 *	74 ± 18 (34)	72 ± 19 (29)	2 ± 18
Run-in 2 *	75 ± 22 (33)	70 ± 20 (29)	5 ± 21
TRT Cycle1	38 ± 14 (26)	50 ± 21 (23)	-12 ± 17
TRT Cycle2	38 ± 19 (26)	50 ± 25 (20)	-12 ± 22
TRT Cycle3	36 ± 13 (25)	52 ± 21 (18)	-17 ± 17
Period 2			
Washout Cycle	60 ± 25 (16)	41 ± 15 (22)	19 ± 20
Baseline	58 ± 23 (16)	40 ± 14 (18)	18 ± 19
TRT Cycle 1	41 ± 22 (16)	48 ± 21 (18)	-7 ± 22
TRT Cycle 2	45 ± 36 (12)	46 ± 18 (15)	-1 ± 28
TRT Cycle 3	38 ± 23 (9)	49 ± 24 (14)	-11 ± 24
* Baseline Value is the average of both Run-in periods			

Figure 5: Study # A07545 - Period 1
DRSP Scores by Cycle

Figure 6: Study # A07545 - Period 2
DRSP Scores by Cycle

In addition to the above analyses, one other analysis was carried out where the period effect was considered in the model.

Tables 11 shows the results based on the Sponsor's and this reviewer's analyses respectively.

Table 11: Sponsor's & Reviewer's Results, Study # A07545
Statistical Comparison between Treatments for Mean Change from Baseline in DRSP Scores
With the Period Effect included in the Model

	Mean ± Std. (n)		Difference (95% CI)	P- Value
	Treatment Arm			
	DRSP/EE	Placebo		
Sponsor's Results*	-22.94 (42)	-10.46 (41)	-12.47 (-18.28, -6.66)	0.0001
Reviewer's Results**	-23.75 (42)	-9.89 (41)	-13.86 (-20.81, -6.91)	0.0001

* Sponsor had used a Proc Mixed with sequence, period, treatment, center, baseline as a covariate and subject as random.
** Reviewer used a Proc Mixed with period, treatment and baseline as covariate, subject as random.

Again, as it can be observed in the above Table, the result achieved by the sponsor is comparable to that of the reviewer's.

3.2 Evaluation of Safety

For information regarding the safety of this product, please refer to the Medical Officer's review.

4. FINDINGS IN SPECIAL SUBGROUPS

4.1 Gender, Race and Age

As the studies are gender-specific and the majority of the subjects are Caucasian (about 91%) and between the ages of 18 to 42, no subgroup analyses are considered necessary.

5. CONCLUSIONS

Study A21566, the placebo controlled, parallel group trial, for the indication of Premenstrual Dysphoric Disorder (PMDD) showed statistically significant superiority, ($p < 0.001$) based on the results submitted by the sponsor. Based on the analysis of the reviewer, using electronic data submitted to the Agency, the results were consistent with those of the sponsor.

Study A07545, the cross-over study, although discontinued prematurely, showed statistically significant results in period one for both sponsor and reviewer ($p \leq 0.05$). The results for period two should be interpreted with caution since problems existed due to drop-outs, possible carry over effect and inability to maintain the randomization (due to drop-outs). Nonetheless, strong results still held for the second period as well ($p=0.001$). Also, when statistical comparison between treatments for mean change from baseline in DRSP scores was estimated with the period effect included in the model, both outcomes from the sponsor and the reviewer were comparable ($p=0.0001$).

/s/
- - - - - - - - - - - - - - - - - - - -
Mike Welch
1/17/2006 03:40:36 PM
BIOMETRICS
Submitted for Shahla Farr.   Concur with review.

S. Edward Nevius
1/18/2006 10:28:13 AM
BIOMETRICS
Concur with review.