Table 22 Pooled Demographic Data

Variable	YAZ (24 days) (N=285)	Placebo (N=267)	Total[a] (N=513)
Age (years)			
n	285	267	513
Mean ± SD	31.2 ± 5.59	32.0 ± 5.57	31.6 ± 5.59
Median	32.0	32.0	32.0
Min – Max	18 – 40	18 – 42	18 – 42
Race (n [%])			
Caucasian	216 (75.8)	207 (77.5)	394 (76.8)
Black	31 (10.9)	24 (9.0)	52 (10.1)
Hispanic	26 (9.1)	25 (9.4)	48 (9.4)
Asian	3 (1.1)	4 (1.5)	6 (1.2)
Other	9 (3.2)	7 (2.6)	13 (2.5)
Height (cm)			
n	284	265	510
Mean ± SD	165.49 ± 6.399	166.05 ± 7.021	165.76 ± 6.706
Median	166.00	166.37	166.03
Min – Max	144.8 – 184.6	144.8 – 194.9	144.8 – 194.9
Weight (kg)			
n	285	264	510
Mean ± SD	70.48 ± 13.676	69.10 ± 13.361	69.81 ± 13.531
Median	68.49	66.23	67.22
Min – Max	44.5 – 108.9	45.7 – 112.0	44.5 – 112.0
BMI (kg/m^2)			
n	284	264	509
Mean ± SD	26.083 ± 4.682	25.377 ± 4.508	25.743 4.608
Median	25.510	24.370	24.800
Min – Max	17.20 – 37.58	14.00 – 36.46	14.00 – 37.58

BMI = body mass index; Max = maximum; Min = minimum; N = total number of subjects treated; n =number of subjects; SD = standard deviation.
[a]Subjects in the crossover study were counted only once in the "Total" column.

Source: Text Table 5, iss.pdf, p24

7.2.1.3 Extent of exposure (dose/duration)

Both studies involved three cycles of treatment with DRSP/EE, administered daily for 24 days of each cycle. The number of cycles of exposure was determined by the number of bleeding start dates entered in subjects' diaries; once a bleeding start date was recorded, the prior cycle was considered to have been completed. Seventy percent of subjects received at least three cycles of DRSP/EE, while 18% and 8% received one and two cycles, respectively (see Table 23).

Table 23 Duration of Exposure in Pooled Sample

Study Phase	Total Exposure in Number of Cycles					Total
	<1 Cycle[a]	1 Cycle	2 Cycles	3 Cycles	4 Cycles	
Phase 3	10	52	23	194	6	285

[a]Includes subjects with possible exposure (drugs dispensed).

Source: Text Table 3, iss.pdf, p 21

7.2.1.4 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No additional sources were used to evaluate safety in this review of the PMDD indication. See the review of NDA 21-676 for further discussion of additional safety data sources used to evaluate safety of this DRSP/EE dose regimen.

7.2.1.5 Other studies

No other studies were submitted.

7.2.1.6 Postmarketing experience

YAZ is not marketed in any country, either for oral contraception or for treatment of PMDD. Postmarketing pharmacoepidemiologic surveillance data for the approved product Yasmin are discussed in the review of NDA 21-676.

7.2.1.7 Literature

The applicant provided many references from the published literature in the Clinical section of the NDA, but did not comprehensively review the literature

7.2.2 Adequacy of Overall Clinical Experience

The overall clinical experience was acceptable. Both studies were based on three-month treatment cycles, the typical duration of trials of the approved SSRIs used for treatment of PMDD. The population studied was appropriately defined and likely to generalize to the population of women likely to seek treatment for PMDD. Study 304049 was a reasonably large, well conducted trial that provided statistical and clinical evidence of efficacy of DRSP/EE in the treatment of PMDD. Study 305141 is limited by the small sample size resulting from the decision to terminate recruitment prior to achieving the targeted number of subjects, and by the high frequency of termination prior to completion of the full cross-over sequence of treatments. However, the reviewer concurs with the FDA statistician that the results of Study 304049 provide acceptable evidence of the efficacy of DRSP/EE in treating symptoms of PMDD.

One study site that participated in both trials experienced serious incidents of misconduct on the part of the study coordinator. However, after a full assessment of all source documents for both trials, it appears that there is minimal impact on the validity of the trial results. This is supported by the consistency between the results when analyzed in the Full Analysis set and in the Per Protocol set.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Data from the preclinical program were initially submitted in NDA 21-098 (Yasmin) for the contraception indication. The pharmacology/toxicology reviewer recommended approval of YAZ in the first cycle based on previous findings of safety and prior approval of Yasmin.

7.2.4 Adequacy of Routine Clinical Testing

In general, the routine evaluation of subjects on the safety parameters incorporated in the trials was adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

The Clinical Pharmacology reviewer found NDA 21-676 acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. NDA 21-873 referenced NDA 21-676 for all human pharmacokinetics

and Biopharmaceutics information, and no changes to the drug product have been made in NDA 21-873 that would impact the original recommendation.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The subject of this NDA is not a new drug. The Applicant was thorough in evaluating the occurrence of potential adverse events associated with DRSP/EE, such as hyperkalemia with adverse cardiovascular sequelae and VTEs.

7.2.7 Assessment of Quality and Completeness of Data

Overall, the data were of sufficient quality to allow an adequate safety review. There was significant attrition of subjects in Study 305141 prior to completion of TP2, but overall, there is an adequate number of subjects (200) contributing safety data over a three month treatment course.

7.2.8 Additional Submissions, Including Safety Update

A safety update was submitted on April 29, 2005; data from this update were incorporated into the preceding safety review. Additional safety updates that pertain to postmarketing surveillance and phase 4 pharmacoepidemiology studies on Yasmin are discussed in the review of NDA 21-676.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no signals of concern in regard to the occurrence of SAEs or changes in vital signs or laboratory evaluations associated with DRSP/EE. Selected adverse events of particular relevance to this product are: intermenstrual bleeding and menorrhagia, nausea, breast pain, decreased libido, emotional lability, and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo and were considered to be drug-related. As noted previously, most of these events are known to be associated with oral contraceptive use, and are labeled in the Yasmin label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data were pooled over Studies 304049 and 305141 for evaluation of adverse events, laboratory evaluations, vital signs and body weight.

7.4.1.1 Pooled data vs. individual study data

Individual study data are reported in Appendices 10.1.9 and 10.2.9. All data reported in the Integrated Safety sections are pooled over both studies.

7.4.1.2 Combining data

Pooled data were obtained by summing the individual events in each of the two phase 3 studies; no weighting was utilized.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only a single dose level was evaluated in the clinical studies, and no PK data to explore exposure were obtained. Dose dependency of adverse findings can therefore not be determined.

7.4.2.2 Explorations for time dependency for adverse findings

Both pivotal studies examined a three-cycle exposure to DRSP/EE. The pattern of withdrawals suggests that subjects are more likely to withdraw from treatment earlier in the course of treatment; however, the specific time dependency of adverse effects was not explored.

7.4.2.3 Explorations for drug-demographic interactions

No subgroup analyses for demographic factors such as race were performed.

7.4.2.4 Explorations for drug-disease interactions

Subjects were generally healthy outside of their PMDD diagnoses. Subjects with hepatic dysfunction or other severe systemic disorders were excluded; therefore impact of DRSP/EE in patients with such concomitant illnesses cannot be assessed.

7.4.2.5 Explorations for drug-drug interactions

See Section 8.2.

7.4.3 Causality Determination

Three classes of adverse events, which appeared more frequently among DRSP/EE subjects, appear causally related to drug treatment: bleeding disorders, breast pain, and mood disorders. These are all adverse effects associated with use of oral contraceptives in general, and are labeled in the current Yasmin labeling. Their occurrence in these trials for the PMDD indication does not suggest a safety profile of greater concern than any other oral contraceptive.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen proposed is DRSP 3 mg/EE 20 μg, administered once daily in tablet form for 24 days, followed by 4 days of inert tablets. The dose was selected based on efficacy for the primary indication, prevention of pregnancy. In earlier studies, 2 mg of DRSP was found to be the threshold dose for inhibition of ovulation, with 3 mg required for reliable inhibition. The EE dose of 20 μg was selected as the lowest dose currently available in marketed contraceptive products.

The 24-day dose regimen was selected to enhance ovarian suppression and to minimize breakthrough symptoms typically experienced during the pill-free interval.

8.2 Drug-Drug Interactions

A drug-drug interaction study with simvastatin was conducted in 24 healthy postmenopausal women, with simvastatin used as a marker substrate for CYP3A4. Subjects were treated in a cross-over manner

with a single 40 mg dose of simvastatin (Treatment A) and a 14-day course of 3 mg DRSP with a single 40 mg dose of simvastatin given on the last day of DRSP treatment (Treatment B). The ratio of $AUC_{(0\text{-}Tlast)}$ for simvastatin (Treatment B/Treatment A) was 115% (90% confidence interval [CI] 90-147%), which did not fall completely within the predefined equivalence interval of 70-143%. Thus, pharmaceutical interaction between DRSP and simvastatin could not be ruled out. The Applicant notes that the sample size may have been too small to account for the high inter-subject variability of simvastatin pharmacokinetics, and does not anticipate any clinically relevant drug-drug interactions between DRSP and CYP3A4 substrates. An additional trial to investigate potential CYP3A4 interactions with DRSP, using midazolam as the CYP3A4 marker substrate was submitted to NDA 21-355 (Angelique, a hormonal treatment for menopausal symptoms which contains the same drug substances as YAZ). This study concluded that DRSP doses up to 3 mg/day did not potently inhibit CYP3A4, and that dose reductions for CYP3A4 substrates would not be necessary when taken concomitantly with DRSP.

An additional study using omeprazole as a marker substrate for CYP2C19 showed no effect of 14 days of DRSP on systemic clearance of the CYP2C19 substrate or metabolic product, nor on clearance of the CYP3A4 metabolic product.

8.3 Special Populations

Race
The population in the combined studies was over 75% Caucasian; no efficacy or safety analyses of racial subgroups were conducted.

Gender & Pediatrics
The proposed indication is for postmenarchal females; as such, it is not anticipated that the drug will be used in prepubertal females or in men.

Renal and Hepatic Impairment
Subjects were generally healthy postmenarchal women age 18 to 42; in fact, women with diabetes, cerebrovascular disease or cardiovascular disease were specifically excluded. In addition, women with laboratory values that would suggest hepatic or renal dysfunction were excluded; therefore the effect of DRSP/EE in patients with such concomitant illnesses cannot be assessed. The proposed labeling would contraindicate DRSP/EE in women with hepatic dysfunction and moderate to severe renal dysfunction, as does the current Yasmin label.

8.4 Pediatrics

A waiver of the requirement for pediatric studies (ages 0 to 11 years) was requested by the Applicant, justified by the small number of patients in this age range who would use the drug for pregnancy prevention or treatment of PMDD.

Medical Reviewer's Comments:

- ***The reviewer agrees that a waiver of pediatric studies is warranted.***

8.5 Advisory Committee Meeting

No Advisory Committee meeting was held to discuss this application.

8.6 Literature Review

A comprehensive review of the literature was not conducted. Individual publications reviewed are discussed and referenced throughout the body of the review.

8.7 Postmarketing Risk Management Plan

The planned post-marketing risk management activity is discussed in the review of NDA 21-676.

8.8 Other Relevant Materials

The Division of Drug Marketing, Advertising and Communications made recommendations which are discussed in Section 9.4. The Division of Surveillance, Research and Communication Support made recommendations regarding patient labeling, which are discussed in Section 9.4. The Division of Medication Errors and Technical Support recommended against the use of the tradename YAZ and made additional recommendations regarding labeling, which are also discussed in Section 9.4.

9 OVERALL ASSESSMENT

9.1 Conclusions

In both studies, the primary efficacy analysis in the Full Analysis set, the ANCOVA modeling the change from baseline to the average over three treatment cycles in the first 21 items of the DRSPS results demonstrated a statistically significant difference between DRSP/EE and placebo groups. The improvement in the DRSP/EE group in Study 304049 was 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects (p=0.0001). In the cross-over trial, Study 305141, where results were calculated by an ANCOVA model that collapsed treatment assignment over treatment period (with treatment sequence as a fixed factor), the improvement in the DRSP/EE group was 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by placebo subjects (p=0.0001). Results were very similar, and remained statistically significant, when analyzed using the per protocol population.

In response to DRUP concerns about the potential for unblinding of subjects to their treatment assignment based upon the effect of DRSP/EE on menstrual bleeding patterns and the impact of potential compromise of blinding on the efficacy findings, the Applicant to provided data concerning the efficacy of DRSP/EE in the first treatment cycle. The effect at the first treatment cycle was statistically significant in both trials: the difference between DRSP/EE and placebo at Cycle 1 in Study 304049 of -8.2 was statistically significant (p=0.0002), as was the difference in Study 305141 of -14, p=0.02) observed in TP1. Since any possible effect on blinding due to noticeable changes in menstrual bleeding profile on DRSP/EE could not have occurred until the first menstrual cycle, demonstration of a statistically significant treatment effect at the luteal phase of Cycle 1 suggests that the efficacy results were not attributable to a possible compromise in blinding.

Statistically significant differences between DRSP/EE and placebo groups were demonstrated for a number of secondary endpoints, typically those which tended to assess symptoms and function over the week preceding menses, rather than over a longer time period. The most consistently positive secondary endpoints were the three functional items on the DRSPS. The finding of a benefit to DRSP/EE treatment on these items is particularly relevant due to their utility in assessing the effects of treatment on social and professional functioning.

DRUP requested that the Applicant show that changes in symptomatology occurring with treatment were of clinical benefit to subjects. The Applicant estimated the MICD using a distribution-based method, which utilizes a calculated effect size independent of the specific measurement instrument used. Effect sizes are used to compare results across studies which may use different instruments; by convention[1], effect sizes of 0.2, 0.5 and 0.8 SD units represent small, medium and large treatment effects. The Applicant presented effect sizes for DRSP/EE in the two studies of approximately 0.4 for Study 304049

and 0.7 for Study 305141, suggesting a moderate treatment effect. The effect sizes demonstrated for treatment with DRSP/EE closely approximate the effect sizes calculated from pooled data for SSRIs. Similarly, comparison of the absolute change from baseline in treatment vs. placebo groups for DRSP/EE and for published trials of fluoxetine and sertraline that used the DRSPS to measure outcome showed that the absolute change in the DRSP/EE trials, particularly in Study 304049, is within the same range as that seen in published SSRI trials, and the difference in response between study drug and placebo is also similar across the drugs.

FDA reviews of the original NDA submissions for the three SSRIs approved for the PMDD indication were utilized to attempt a comparison of the DRSP/EE results to those attained by the SSRIs. In the most relevant comparison, to the fluoxetine luteal phase dosing trial, which used the identical outcome measure, over the same treatment period, the changes from baseline with treatment in DRSPS score for the study drug were -28 to -31 depending on fluoxetine dose, compared to -37.5 for Study 304049 and -17 to -34 for Study 305141, depending on treatment sequence. The magnitude of the difference between study drug and placebo in change from baseline in DRSPS 21 scores was similar (5 to 8 for fluoxetine, 7.5 for Study 304049, and 9.5 to 14 for Study 305141). In the SSRI trial, this treatment effect was judged to provide adequate evidence of efficacy for intermittently-dosed fluoxetine, supporting a recommendation for approvability.

In the present Application, the FDA statistician reviewed the two phase 3 studies and concluded, based on her reanalysis of the data, that Study 304049 showed statistically significant superiority of DRSP/EE to placebo in change from baseline in DRSPS scores ($p < 0.005$), as did Study 305141 ($p = 0.02$ at TP1, $p = 0.001$ at TP2). The statistician stated that the drop-out rate, possible carry-over effect and difficulty maintaining the randomization, all pose problems for TP2, but that the results are strongly significant.

The statistical reviewer noted that the statistically significant difference between the two treatment arms in Study 305141 at the washout (baseline) cycle preceding TP2 may be an indication that the duration of washout was not sufficient to eliminate the drug carry-over effect. Given the Applicant's use of the washout cycle score as the baseline to which TP2 scores were compared, obtaining the TP2 baseline with inadequate washout would result in subjects who crossed-over from DRSPS/EE to placebo starting at a lower DRSPS score, thus making it more difficult to demonstrate improvement from baseline in TP2. This would result in a larger difference between DRSP/EE and placebo in change from baseline for TP2. However, it is statistically appropriate to analyze only the first phase of a cross-over study design, as randomization is preserved at this point, despite later drop-outs. In this case, a statistically significant result was obtained in TP1 and the results calculated overall by drug exposure, controlling for sequence of treatment are statistically significant, indicating a benefit from DRSP/EE over and above that which could be attributed to inadequate washout.

The safety profile for DRSP/EE as evidenced in these trials is acceptable. No deaths or VTEs occurred over the three cycles of treatments. Few SAEs occurred, and these were not believed to be attributable to DRSP/EE. The adverse events that occurred more commonly among DRSP/EE subjects are those that tend to be associated with oral contraceptive use in general. There was no indication of any cardiovascular adverse events that might be attributable to hyperkalemia.

Evaluation of laboratory assessments showed that a small but increased percent of DRSP/EE subjects as compared to placebo subjects had increases in potassium level to outside of the normal range over the course of treatment. However, these elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of DRSP/EE. The overall mean change in potassium level with treatment was minimal and similar to that experienced in the placebo group. There did not appear to be an increased risk of renal impairment with DRSP/EE use; however, it appears that subjects with mild renal impairment at baseline who take DRSP/EE may experience greater

mean change in potassium than do placebo subjects, or subjects with normal renal function. As is recognized for oral contraceptives generally, DRSP/EE had an adverse impact on lipids, primarily affecting triglycerides and total cholesterol, with almost double the percent of DRSP/EE as opposed to placebo subjects shifting from normal baseline values to high values on treatment.

Vital signs measurements did not demonstrate clinically relevant changes from baseline in either treatment group.

While the treatment effect of DRSP/EE on symptoms of PMDD may be seen as moderate, it has been demonstrated to be similar to that observed with use of the SSRIs currently approved for the PMDD indication. Availability of an oral contraceptive product for treatment of PMDD would offer several advantages over use of an SSRI: in women already using oral contraception, a single drug could address both health needs, and potential adverse effects of SSRIs, ranging from sexual dysfunction to possible increased suicidality, could be avoided.

9.2 Recommendation on Regulatory Action

It is recommended that NDA 21-873, DRSP (3 mg)/EE (20 μg) oral tablets (YAZ), be approved for the indication of treatment of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who chose to use an oral contraceptive as their method of contraception," contingent upon submission of acceptable labeling by the Applicant and approval of NDA 21-676 for the indication of prevention of pregnancy.

The reviewer finds that:

- Adequate statistical evidence of efficacy relative to placebo has been demonstrated for DRSP/EE in treatment of PMDD symptoms.
- The clinical benefit of treatment with DRSP/EE has been satisfactorily indicated by statistically significant improvement on several secondary endpoints that assess social and professional functioning and global improvement.
- The magnitude of the treatment effect appears to be consistent with that attributable to treatment with the three SSRIs approved for treatment of PMDD.
- The safety data do not raise concern for a safety profile discrepant from that of the approved product, Yasmin, and, in fact, the lower total exposure to EE afforded by use of YAZ as compared to Yasmin may offer a safety advantage.
- Considering the risk/benefit profiles of DRSP/EE and the approved SSRI treatments, approval of this product would offer women with PMDD who desire oral contraception a useful treatment alternative.

9.3 Recommendation on Postmarketing Actions

The proposed risk management activity and postmarketing safety study are acceptable, and are discussed in the review of NDA 21-676 (DRSP/EE for prevention of pregnancy).

9.3.1 Risk Management Activity

The applicant has committed (letter date 17-Nov-2005) to conducting an educational program for healthcare providers and a risk management plan, similar to that conducted for the presently marketed DRSP-containing product (Yasmin) for 3 years after the launch of YAZ in the U.S.

9.3.2 Required Phase 4 Commitments

No phase 4 commitments are requested. As discussed in the review of NDA 21-676, the Applicant has committed to conducting a large prospective phase 4 postmarketing safety study with YAZ, similar to the ongoing European Active Surveillance Study (EURAS) assessing risk of arterial and venous thromboembolic events in users of Yasmin, as compared to users of other oral contraceptives. The proposed study for YAZ will include both U.S. and European sites, and plans to recruit 50,000 women who will be followed semi-annually for three years.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

A joint label for the oral contraception and PMDD is proposed by the Applicant. This is acceptable to the reviewer.

The Division of Surveillance, Research, and Communication Support recommended that patient labeling follow the March 2004 Draft Guidance on Labeling for Combined Oral Contraceptives, and that upper case lettering be avoided except for the tradename.

The Division of Medication Errors and Technical Support recommended elimination of terminal zeroes in doses and requested that the Brief Summary and Detailed Patient Package Inserts be revised to improve readability.

The following areas of the label specific to the PMDD indication were addressed by the reviewer:

- **Indications and Usage** – indication revised to state: YAZ is indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception.
- **Clinical Trials** – Premenstrual Dysphoric Disorder: clarified how PMDD is diagnosed; revised description of clinical trials
- **Brief Summary Patient Package Insert & Detailed Patient Package Insert**: the following paragraph was added:

These comments will be conveyed to the Applicant.

9.5 Comments to Applicant

There are no additional comments to the Applicant.

10 APPENDICES

10.1 Review of Individual Study Report for Protocol 304049 (Report A21566)

10.1.1 Summary

Title: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 µg (as Beta-Cyclodextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)" dated 19 November 2004.

Six amendments were made to Study 304049.

First patient entered: January 2001

Last patient completed: February 2004

10.1.2 Objectives

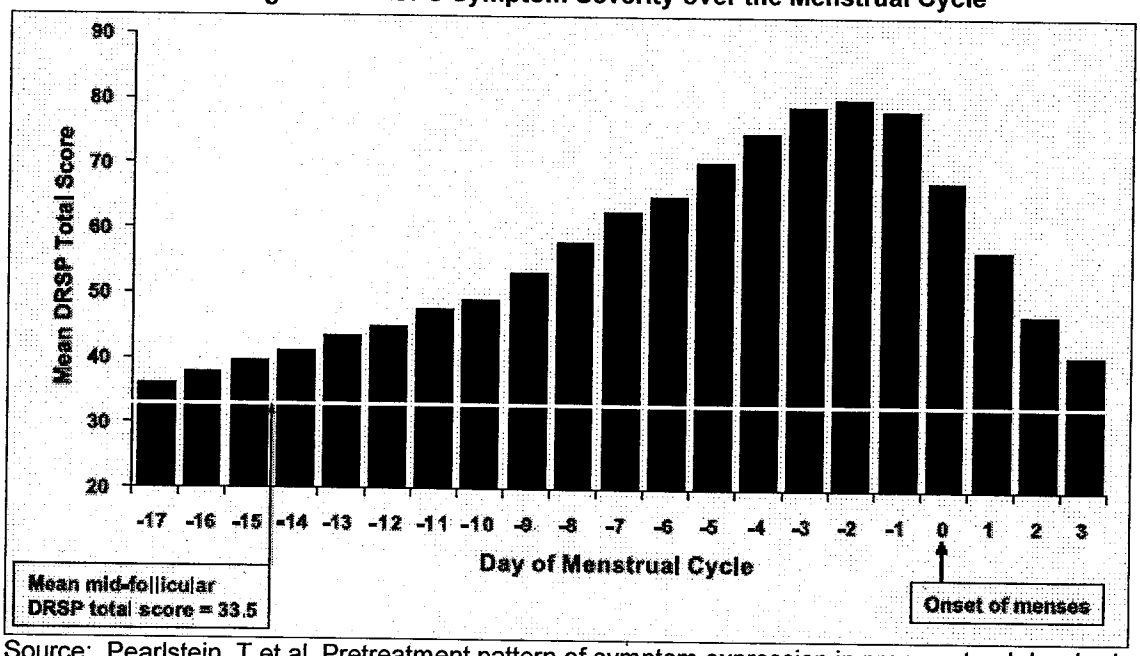
The primary objectives of this study were to assess the efficacy and safety of DRSP/EE compared to placebo in treating the symptoms of PMDD. Efficacy was evaluated by looking at change from baseline in the sum of the averages over the five days preceding menses in the first 21 items on the DRSPS, averaged over the three treatment cycles.

Medical Reviewer's Comments:

- ***In discussions with the Applicant during development of these protocols, DNDP recommended that luteal phase DRSPS ratings be obtained over the full seven days of the late luteal phase. Although subjects completed this instrument daily, the Applicant has only provided data over the five days preceding menses. However, the reviewer has been unable to find any data indicating a time trend in symptomatology within the luteal phase that would suggest that use of the last five days would misrepresent the level of symptomatology experienced over the seven day phase. In fact, a recent study[4] of 276 women meeting DSM-IV criteria for PMDD measured symptomatology with the DRSPS prospectively for two cycles before the women initiated SSRI treatment. These data suggest that the five days prior to onset of menses encompass the maximal levels of symptomatology seen in the luteal phase (see Figure 4).***

APPEARS THIS WAY
ON ORIGINAL

Figure 4 DRSPS Symptom Severity over the Menstrual Cycle



Source: Pearlstein, T et al Pretreatment pattern of symptom expression in premenstrual dysphoric disorder. J Affect Disord 85: 275-82, 2005

10.1.3 Overall Design

This phase 3, U.S. multicenter, randomized, double-blind, placebo-controlled three month treatment duration study was designed to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in treating symptoms of PMDD. Subjects diagnosed with PMDD by DSM-IV criteria were enrolled in a study consisting of a two cycle run-in phase followed by a treatment phase lasting three menstrual cycles. Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio.

The study was conducted at 64 sites in the U.S, although 77 sites participated in screening subjects. The recruitment goal was 408 subjects; actual enrollment was 232 subjects to DRSP/EE and 218 to placebo. The planned sample size was to provide 85% power with an alpha level of 0.05 to detect a difference of 6.5 points (SD 18) in the DRSPS score change from baseline between treatment and placebo arms, assuming a 30% drop-out rate.

Medical Reviewer's Comments:

- ***No justification of the choice of 6.5 points as the detectable difference for which the study was powered was provided by the Applicant. However, this difference was within the general range of treatment – placebo differences noted in studies of SSRIs for PMDD.***

10.1.4 Study Procedures and Conduct

10.1.4.1 Schedule of Study Assessments

Subjects were screened for eligibility at Visit 1 and procedures indicated in Table 24 were performed. Subjects were historically screened based on DSM-IV criteria for PMDD (see Table 25), and those with past and present psychiatric disorders other than PMDD were excluded based upon the Structured Clinical Interview for DSM-IV (SCID), which was preferably administered at Visit 3, but could be administered

as early as Visit 1 or 2. Subjects were then instructed to record daily ratings of PMDD symptoms using the DRSPS instrument, beginning on the first day of the next menses following Visit 1. Two run-in visits occurred at days 5-10 of menstrual cycles 1 (Visit 2) and 2 (Visit 3) following screening. At both visits, the completed DRSPS ratings were reviewed, and at Visit 2, eligibility was reconfirmed, and the PMTS, SF-36 and Q-LES-Q instruments were administered. Physical and gynecological exams and laboratory assessments were performed at Visit 3. Three clinical visits occurred during the treatment phase: Visits 4-6 occurred on days 1-3 of cycle 3 (treatment cycle 1) and days 1-4 of cycles 4 and 5 (treatment cycles 2 and 3), respectively; Visit 7 occurred on days 5-10 of the first post-treatment menstrual cycle. At Visit 4, subjects were randomized, and provided with 3 cycles of study drug. At this visit, and at each monthly visit thereafter, efficacy and safety measures were obtained as indicated in the Schedule of Assessments.

Table 24 Study 304049: Schedule of Study Assessments

Cycle day	Screen Visit (Visit 1) Any day	Run-in Cycle 1 (Visit 2) 5-10	Run-in Cycle 2 (Visit 3) 5-10	Treatment Cycle 1 (Visit 4) *1-3*	Treatment Cycle 2 (Visit 5) 1-4	Treatment Cycle 3 (Visit 6) 1-4	Post Treatment (Visit 7) '5-10'
	May have been combined visit b						
Informed consent	X						
Randomization				X			
In/exclusion criteria	X	**X**	**X**	X			
Instruct (I)/review (R)/collect (C) DRSPS	I	R	R, C	R, C	R, C	R, C	R, C
History and baseline information c	X						
Weight, blood pressure, heart rate, temperature		X d	X	X	X	X	X
Contraceptive method	X	X	X	X	X	X	X
DSM-IV criteria	X-history			X-prospective			
SCID e	X	X	**X**				
Pregnancy test (urine [U]/serum [S])		X-U	X-S	X-U	X-S	**X-S f**	X-S
Concomitant medication	X	X	X	X	X	X	X
Adverse events		**X**	X	X	X	X	X
Endocervical sample			X				
Physical and gynecological exams, Pap smear			X				X
Hematology/Chemistry**g**			X		X		X
Urinalysis			X				'X'
CGI				He	X	X	X
PMTS scales, SF-36, Endicott Q-LES-Q		X		X			X
Drug dispensed/returned				X-dispensed	X-returned	X-returned	X-returned

*a*The final visit procedures were performed upon withdrawal of a subject from the study; *b If visit 1 was on cycle day 1-6, visit 2 procedures may have been performed at visit 1 and the visit 2 window would include cycle day 1-4;* c Included medical, surgical, smoking, gynecological, medication, and menstrual histories; date of birth; and ethnic group; *d* At visit 2, height was also measured and BMI calculated. e **The SCID was preferably administered at visit 3, but alternatively could have been administered at visit 1 or 2;** f **A serum pregnancy test was performed if no menstrual period;** g T3, T4, free thyroxine index, and **TSH** at visit 3 only; *h* Investigator's assessment only for "Severity of illness;". Note: The **bolded** assessments were added with protocol amendment 1; 'text in quotation marks' indicates a change with amendment 2; *italicized text* indicates a change with amendment 6. See Section 9.8 for details.

Source: Text Table 2, a21556.pdf, p 26

Table 25 DSM-IV Criteria for PMDD

A. In most menstrual cycles during the past year, the subject must have had 5 or more of the following 11 symptoms present for most of the time during the last week of the luteal phase, which began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses:
1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feeling of being "keyed up" or "on edge"
3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. Persistent and marked anger or irritability or increase of interpersonal conflicts
In addition, one or more of the following symptoms may have been present:
5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. A subjective sense of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain
B. The disturbances must have markedly interfered with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school)
C. The disturbances were not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder
Criteria A, B and C must have been confirmed by prospective daily ratings during at least 2 consecutive symptomatic cycles. (The diagnosis may have been made provisionally prior to this confirmation.)

Source: a21556.pdf, pp 21-2

10.1.5 Study Drug

10.1.5.1 Dose Selection

The drug studied was DRSP 3 mg/EE 20 µg, administered for 24 days, followed by 4 days of inert tablets. This regimen, which contains a lower daily dose of EE and longer duration of treatment than that in the marketed oral contraceptive, Yasmin, was the subject of an NDA for an indication of pregnancy prevention. Reliable inhibition of ovulation has been demonstrated to require a 3 mg dose of DRSP. The 20 µg dose of EE is the lowest available among marketed oral products. The Applicant believes that the longer duration of treatment in the 24-day regimen would likely be of benefit in treating symptoms of PMDD.

Subjects in the placebo arm received a daily placebo tablet for all 28 days of each cycle.

Medical Reviewer's Comment:

- ***The dose selection was not directly based on the drug's effect on PMDD symptoms. While suppression of ovulation is a useful pharmacodynamic measure for DRSP/EE's contraceptive indication, it is a surrogate marker of unproven validity for the drug's utility for the PMDD indication. Since PMDD is a secondary indication, the selection of dose is based on the primary indication (prevention of pregnancy).***

10.1.5.2 Choice of Comparator

DRSP/EE was compared against placebo due to the known high rate of nonspecific response to treatment seen in PMDD.

10.1.5.3 Assignment to Study Drug

Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio at Visit 4, based on permuted block randomization.

10.1.6 Patient Population

Subjects in this study were women with PMDD diagnosed by the DSM-IV criteria, as observed over two menstrual cycles.

10.1.7 Inclusion and Exclusion Criteria

The DRSPS instrument, used extensively in determining eligibility for enrollment, is displayed in Table 26. The degree to which the subject experienced each item is scored from 1 ("not at all") to 6 ("extreme"). Each set of items with the same number is considered a "distinct item" for eligibility purposes.

Table 26 DRSPS

Items are rated on a scale from 1 (not at all) to 6 (extreme)	
1a	Felt depressed, sad, "down," or "blue"
1b	Felt hopeless
1c	Felt worthless or guilty
2	Felt anxious, tense, "keyed up," or "on edge"
3a	Had mood swings (e.g., suddenly felt tearful or sad)
3b	Was more sensitive to rejection or my feelings were easily hurt
4a	Felt angry, irritable
4b	Had conflicts or problems with people
5	Had less interest in usual activities (e.g., work, school, friends, hobbies)
6	Had difficulty concentrating
*7	Felt lethargic, tired, fatigued or had a lack of energy
8a	Had increased appetite or overate
8b	Had cravings for specific foods
*9a	Slept more, took naps, found it hard to get up when intended
*9b	Had trouble getting to sleep or staying asleep
10a	Felt overwhelmed or that I could not cope
10b	Felt out of control
*11a	Had breast tenderness
*11b	Had breast swelling, felt "bloated" or had weight gain
*11c	Had headache
*11d	Had joint or muscle pain
Functional impairment items: • At work, at school, at home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency • At least one of the problems noted above interfered with hobbies or social activities (e.g., avoid or do less) • At least one of the problems noted above interfered with relationships with others	

* physical symptom
Source: a21556.pdf, pp 36-7

Inclusion Criteria

- PMDD by DSM-IV criteria
  - At screening, by history
  - At the end of the second run-in cycle, by review of symptom records
- Any 5 distinct items, without overlap, on the DRSPS (see Table 26) (each of the 2 consecutive baseline run-in cycles must have fulfilled the following criterion):
  - Luteal phase daily average ≥3.0. At least one item must have represented a non-physical symptom
- DSRP scale (each of the 2 consecutive baseline run-in cycles must have fulfilled the following criteria):
  - Follicular phase daily average score of ≤2.5 for each item on the DRSPS for nonphysical symptoms only. However, only one of the physical symptoms that were >2.5 in the follicular phase could have been a symptom in the 5 items needed for the inclusion criterion above. The average was to be computed for days 6-10 of the cycle, and entries in the dairy must have been present for at least 3 of these days for the item to be used as an inclusion criterion for that month.
  - Late luteal phase daily average score at least twice as high as the corresponding follicular phase daily average score for 3 of the 5 distinct items without overlap. At least one item must have represented a nonphysical symptom.
  - Functional impairment items required a score of ≥3 on at least 1 of the 3 impairment items for ≥2 luteal days
- Absence of an existing and/or a history of the following Axis I disorders during the last 2 years based on the SCID:
  - Major depressive disorder
  - Anxiety disorder (panic, obsessive-compulsive, posttraumatic stress)
  - Eating disorder
  - Drug and/or alcohol disorder
- Absence of an existing and/or a history (lifelong) of the following Axis I disorders based on the SCID:
  - Bipolar disorder
  - Psychotic disorder
  - Somatoform disorder
  - Dysthymic disorder
- Healthy volunteer
- 18-40 years, smokers maximum of 34 at inclusion
- Non-suspicious Pap smear within 6 months before study medication. For an ASCUS Pap, either a negative HPV or benign subtype required on HPV testing. Any results worse than LGSIL excluded.
- No oral contraceptives for at least 3 months prior to enrollment
- At least 3 menstrual cycles subsequent to delivery, abortion or lactation before the start of qualification
- Regular menstrual cycles (length between 25-34 days) in the 3 month period preceding qualification
- Negative pregnancy test before first dose
- All subjects needing contraception to use a barrier method during the study
- Signed informed consent
- Would comply with protocol

Exclusion Criteria

- Any formal psychotherapeutic counseling within 1 month of screening, or used medication for PMS or PMDD, including hormones, bromocriptine, GnRH agonists, Vitamin B6 (> 100 mg), calcium supplements (>1500 mg/day), anxiolytics and antidepressants during the 3 months prior to screening Visit 1
- Used sleeping medication, including melatonin, more than 3 days per month
- Pregnant or lactating
- Known hypersensitivity to any of the study drug ingredients
- Any disease or condition that could compromise the function of body systems that could result in altered absorption, excessive accumulation, impaired metabolism or altered excretion of the study drug
- Severe systemic disease that might interfere with conduct of the study or interpretation of results
- Uncontrolled thyroid disorder
- Current or history of clinically significant depression in the past 2 years
- Abnormal, clinically significant findings which could worsen under hormonal treatment
- Use of an experimental drug or participation in another clinical trials within 3 months prior to enrollment
- Liver disease: previous, acute and chronic progressive liver diseases. An interval of at least 6 months required between resolution of viral hepatitis and beginning of study drug intake
- Vascular disease: existing or previous venous or arterial thromboembolic diseases or any condition that could increase the risk of any of the above mentioned disorders (including coagulopathies, hereditary deficiencies, family history, specific heart diseases, cardiac or renal dysfunction and clinically significant varicose veins or previous phlebitis)
- Uncontrolled hypertension (>140/90) or medication for hypertension
- Kown diabetes, blood glucose > 140 mg/dl
- Sickle cell anemia
- Clinically significant abnormal lipid metabolism
- History of estrogen-related malignancies, including breast, endometrial and ovarian. Women with other malignancies/premalignancies eligible for inclusion if recurrence-free for at least 5 years
- History, current or suspicion of: pemphigoid gestations, otosclerosis, endometrial hyperplasia, complicated migraine, genital bleeding of unknown origin, fibroids or kidney disease with impaired renal function
- Use of illicit drugs, alcohol or medicine abuse (e.g., laxatives)
- Use of additional sex steroids, hydantoins, barbiturates, Phenobarbital, phenytoin, primidone, carbemazepine, rifampin, Ritalin, herbal products or dietary supplements for treatment of PMS/PMDD, or continuous use of antibiotics for more than 10 days
- Use of oral contraceptives, injectable estrogens, progestogens or androgens during 3-month period prior to screening; used hormonal contraceptive implant within 1 year, other hormonal contraceptive methods such as hormonal IUD
- Have used or are using Accutane within 30 days; medication, herbals or over the counter formulas to control weight gain or aid weight loss, use of calcium supplements and/or Vitamin B6 if not used during the qualification phase or a change in dosage
- BMI ≥35
- History of porphyria
- History of herpes of pregnancy

- Positive Gonorrhea or Chlamydia test (if treated, with negative repeat culture, could be included)
- Clinically relevant pathological safety laboratory results
- Previous participation in a study involving the same or similar medication for treatment of PMS

10.1.7.1 Demographics and Baseline Disease Characteristics

Sixty-four US sites each enrolled 1 to 40 subjects. Of the 450 subjects randomized, 449 received at least one dose of study medication and therefore constitute the ITT population (232 DRSP/EE, 218 placebo), which was used for safety and efficacy assessments. A single DRSP/EE subject never took study drug. The "Per Protocol" (PP) population, defined as subjects took no prohibited medications, had ≥ 75% compliance, and had no major violations of inclusion/exclusion criteria, consisted of 324 subjects (158 DRSP/EE, 166 placebo).

Demographic characteristics are summarized in Subjects' baseline **DRSPS scores are discussed in Section 10.1.8.1. There were no significant differences at baseline between the scores on the first 21 items in the two treatment arms.**

Medical Reviewer's Comments:

- ***The treatment groups appear comparable.***

Table 27. There were statistically significant differences between the groups on mean age, with the DRSP/EE group being one year younger, and on BMI, with the DRSP/EE subjects being almost one kg/m^2 greater than placebo subjects on average.

Medical Reviewer's Comment:

- ***The younger mean age in the DRSP/EE group might be associated with disease of shorter duration, which could be less refractory to treatment. However, this is not supported by data in Table 30 which demonstrates equivalent DRSPS scores at baseline. Information on the interval since diagnosis in each group would be of interest.***

Subjects' baseline DRSPS scores are discussed in Section 10.1.8.1. There were no significant differences at baseline between the scores on the first 21 items in the two treatment arms.

Medical Reviewer's Comments:

- ***The treatment groups appear comparable.***

Table 27 Study 304049: Demographic Characteristics of ITT Population

Variable	Statistics/Class	Treatment Group		Total
		DRSP/EE	Placebo	
		N = 231	N = 218	
Age (years)	n	231	218	449
	Mean ±SD	31.0 ±5.63	32.0 ±5.48	31.5 ±5.58
	Median	31.0	32.0	32.0
	Minimum-Maximum	18 - 40	18 - 42	18 – 42
Ethnic group (n [%])	Caucasian	176 (76.19%)	170 (77.98%)	346 (77.06%)
	Black	25 (10.82%)	20 (9.17%)	45 (10.02%)
	Hispanic	22 (9.52%)	21 (9.63%)	43 (9.58%)
	Asian	2 (0.87%)	3 (1.38%)	5 (1.11%)
	Other	6 (2.60%)	4 (1.83%)	10 (2.23%)
Weight (kg)	n	230	215	445
	Mean ±SD	70.64 ±13.204	68.43 ±12.892	69.57 ±13.087
	Median	68.95	65.77	67.13
	Minimum-Maximum	44.5 – 108.9	45.8 – 112.0	44.5 – 112.0
Height (cm)	n	230	216	446
	Mean ±SD	165.95 ±6.191	166.40 ±7.042	166.17 ±6.613
	Median	166.67	166.67	166.67
	Minimum-Maximum	151.3 – 184.6	146.2 – 194.9	146.2 – 194.9
BMI (kg/m 2)	n	230	215	445
	Mean ±SD	26.088 ±4.561	25.110 ±4.294	25.616 ±4.456
	Median	25.935	24.290	24.790
	Minimum-Maximum	17.85 – 37.58 a	14.00 – 36.46 b	14.00 – 37.58

Source: Text Table 6, a21566.pdf, p 80

10.1.7.2 Withdrawals, compliance, and protocol violations

Seventy-one DRSP/EE (30.6%) and 51 placebo subjects (23.4%) discontinued the trial prior to completing the full six months. Reasons for withdrawal are shown in Table 28. In total, 36 DRSP/EE subjects and 9 placebo subjects withdrew due to adverse events during the trial (see Section 10.1.9.2).

Medical Reviewer's Comment:

- ***The most common adverse events leading to differential withdrawal in the DRSP/EE and placebo groups tend to be side effects commonly associated with oral contraceptives, including intermenstrual bleeding, breast tenderness and mood changes. They do not suggest a safety profile of greater concern than any other oral contraceptive.***
- ***No additional information clarifying the reason for withdrawal of consent was provided.***

Table 28 Study 304049: Detailed Reason for Withdrawal from Treatment

Patient Disposition	Study 304049			
	DRSP/EE N=232		Placebo N=218	
	N	%	N	%
Completed Treatment	161	69.4	167	76.6
Withdrew from Treatment	71	30.6	51	23.4
Reason for Withdrawal				
Lost to follow-up	13	5.6	14	6.4
Adverse event	36	15.5	9	4.1
Lack of efficacy	1	0.4	-	--
Protocol violation	5	2.2	9	4.1
Consent withdrawn	13*	5.6	17	7.7
Pregnancy	1	0.4	-	--
Other**	2	0.9	2	0.9

* includes single subject who never took study drug
** includes: subject out of window, noncompliance, subject lost diary/month 3 medication, subject moved out of state
Source: Based on Text Figure 1, a21566.pdf, p 73

Compliance was based upon daily recording of tablet intake in subject diaries, and by return of unused or partially used blister packs at the clinical visits. Compliance was defined as the number of pills taken, divided by the number of days between first and last day of drug administration, as recorded in the dairy. Mean compliance was 98% in both the DRSP/EE and placebo groups; 91% of DRSP/EE subjects were ≥ 75% compliant, as were 90% of placebo subjects.

Protocol violations occurred in 195 DRSP/EE subjects (84%) and in 177 placebo subjects (81%), with major deviations in 23% of the DRSP/EE group and in 19% of the placebo group. These 95 subjects with major protocol violations were excluded from the Per Protocol analysis. Major protocol violations included (numbers total >95 since some subjects had multiple violations):

- Deviations in entry criteria
  - 37 violations occurred in DRSP/EE subjects
  - 29 violations occurred in placebo subjects
- Randomization/registration error
  - 1 violation occurred in DRSP/EE subject
  - 2 violations occurred in placebo subjects
- Treatment/procedure deviations (included <75% compliance, taking multiple pills on one or more days and lack of confirmation of diary entries for 4 days)
  - 23 violations occurred in DRSP/EE subjects
  - 22 violations occurred in placebo subjects
- Use of excluded concomitant medication
  - 5 violations each occurred in DRSP/EE and placebo subjects

Medical Reviewer Comment:

- ***The majority of the entry criteria violations related to 44 subjects who did not meet the severity criteria at the baseline and/or randomization visits. Relatively little impact on study results is attributed to these violations, as 26 of these subjects withdrew early from treatment.***

10.1.8 Efficacy

10.1.8.1 Key Efficacy Assessments

Eight instruments used to assess efficacy in this trial are summarized in Table 29 . The DRSPS was used to generate the primary efficacy endpoint, the change from baseline in the luteal phase average over three treatment cycles of the first 21 items of the instrument. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. Items were rated on a scale from 1 (not at all) to 6 (extreme), thus a maximum score of 126 was possible.

Table 29 Summary of Efficacy Scales

Scale	Summary	Frequency of Usage
DRSPS	(a) documents daily symptom severity by 11 distinct categories with 21 individual items (b) 3 functional impairment items	daily
CGI – global improvement	evaluated degree of improvement; investigator-rated and self-rated	visits 5 – 7
CGI – efficacy index	matrix of degrees of therapeutic effects versus side effects; investigator-rated	visits 5 – 7
CGI – severity of illness	assessed degree of mental illness; investigator-rated	visits 4 – 7
SF-36 health survey	evaluated quality of life: 36 individual items; evaluated mental health and physical health	visits 2, 4, and 7
Endicott Q-LES-Q	assessed degree of enjoyment and satisfaction experienced during the week prior to menses 16 items; self-rated	visits 2, 4, and 7
PMTS-O	assessed 10 different types of symptoms 10 items; investigator-rated	visits 2, 4, and 7
PMTS-SR	assessed 10 different types of symptoms 36 items; self-rated	visits 2, 4, and 7

DRSPS = Daily Record of Severity of Problems scale;
CGI = Clinical Global Impressions
Q-LES-Q = Quality of Life Enjoyment and Satisfaction questionnaire.
PMTS-O = Premenstrual Tension Syndrome scale, observer-rated;
PMTS-SR = Premenstrual Tension Syndrome scale, self-rated

Source: Text Table 3, a21566.pdf, pp 36

Additional secondary endpoints were based on the Clinical Global Impressions scale (CGI), the SF-36, the Endicott Q-LES-Q, and the PMTS. The CGI evaluated the subject's status in the week prior to menses, and provided three investigator-rated parameters and one subject-rated assessment of global improvement. The SF-36 is a self-administered quality of life instrument with response options ranging from "yes/no" to a six-point scale. Status was evaluated over varying time periods, most commonly over the past four weeks. The Q-LES-Q is also a self-rated quality of life questionnaire which subjects answered regarding their status during the week prior to menses, rated on a scale from 1 (very poor) to 5 (very good). The PMTS had a scale rated by the investigator and one rated by the subject for the week prior to the onset of menses. Response options for the investigator-rated scale ranged from 0-2 or 0-4, while subject responses were "yes/no."

The primary efficacy analysis was done on the "full analysis" set, defined as all randomized subjects who received at least one dose of study medication. "Per protocol analysis," based on a subset of the full

analysis set (excluding subjects who took any prohibited medications, had <75% compliance, had major violations of inclusion/exclusion criteria, had a major protocol violation or failed to provide a DRSPS score for at least one treatment cycle) was also used to analyze the primary efficacy variable.

Medical Reviewer's Comment:

- ***The Applicant confirmed on January 6, 2006 that subjects who took at least one dose of study drug but withdrew before recording luteal phase data for Treatment Cycle 1 were not included in the efficacy analyses. Thus, the "Full Analysis" set is actually a modified Intent to Treat (ITT) population. In Study 304049, 41 DRSP/EE subjects and 23 placebo subjects were excluded on this basis.***
- ***Since the effect of the drug would not be expected to impact DRSPS scores in advance of the luteal phase, the reviewer finds the use of a modified ITT analysis set acceptable.***

10.1.8.2 Pharmacokinetic Assessments

Pharmacokinetic sampling was not done in this study.

10.1.8.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was the change from baseline in the average over three treatment cycles of the first 21 items of the DRSPS. For each cycle, the first 21 items were averaged over the five days preceding menses, and then summed. The primary efficacy variable was the difference between treatment arms in change in the average of the non-missing treatment cycle scores (from 1-3 scores averaged per subject) from the baseline score, which was averaged over the two run-in cycles.

Cycles were based on the first recording of menses in the diary; for subjects with any amenorrhea, where cycle stop/start dates could not be determined, determination of the dates when pills 20-24 were taken was made from manual review of the diary prior to unblinding. If an item was missing for a day during the five days preceding menses, the missing item was imputed by averaging the two non-missing bordering days' values. Thus, data missing from day 1 or 5 prior to menses could not be imputed due to lack of qualifying bordering days. If more than two days of an item were missing after the above imputation was done, the item average was set as missing.

Medical Reviewer's Comments:

- ***DNDP had recommended that luteal phase DRSPS ratings be obtained over the full seven days of the late phase, and requested that the Applicant justify any decision to use less than the full seven day period. However, as noted in the Reviewer's Comment in Section 10.1.2, the reviewer does not believe that use of the shorter luteal phase period compromises the validity of the data.***
- ***The Division had recommended that missing data be imputed by averaging <u>all</u> non-missing data points for that cycle; instead the Applicant has averaged only the two bordering days' data. However, in each cycle, 94-98% of subjects had no imputed scores, so this difference in methodology is unlikely to have any effect on the results.***

Table 30 displays the DRSPS scores by treatment group and cycle. The difference between treatment arms on the mean scores over the two run-in cycles were not statistically significant (p=0.57).

Table 30 DRSPS Scores by Treatment Group and Cycle

Cycle		Treatment Group DRSP/EE N = 231	Placebo N = 218
Run-in cycle 1	n	231	215
	Mean ± SD	76.14 ± 18.635	77.84 ± 19.911
	Median	74.20	76.20
	Minimum – Maximum	35.6 – 126.0	27.8 – 125.2
Run-in cycle 2	n	223	208
	Mean ± SD	78.96 ± 18.570	79.28 ± 19.917
	Median	76.60	79.20
	Minimum – Maximum	38.4 – 126.0	30.6 – 126.0
Treatment cycle 1	n	190	195
	Mean ± SD	42.94 ± 19.731	51.39 ± 24.477
	Median	36.50	44.60
	Minimum – Maximum	21.0 – 126.0	21.0 – 126.0
Treatment cycle 2	n	165	170
	Mean ± SD	39.78 ± 18.774	46.63 ± 23.013
	Median	32.20	40.30
	Minimum – Maximum	21.0 – 107.0	21.0 – 121.8
Treatment cycle 3	n	138	130
	Mean ± SD	37.60 ± 17.217	47.31 ± 24.796
	Median	30.90	39.30
	Minimum – Maximum	21.0 – 101.8	21.0 – 117.4

Source: Text Table 8, a21566.pdf, pp 84

Table 31 shows the adjusted mean baseline score and the scores at each treatment cycle by treatment arm, based on the ANCOVA model. In both DRSP/EE and placebo groups, the change from baseline at each treatment cycle was statistically significant ($p<0.0001$). The ANCOVA comparing the difference between DRSP/EE and placebo groups in the adjusted mean change from baseline averaged over the three treatment cycles found that the improvement in the DRSP/EE group was 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects ($p=0.0001$). Results were very similar, with the same p values, when analyzed using the per protocol population.

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Table 31 DRSPS Score & Change from Baseline by Treatment Group and Cycle

	Statistic	Baseline average	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 average
DRSP/EE	N	190	190	165	138	190
	Mean (SD)	77.4 (16.7)	-34.5 (22.2)	-37.1 (21.4)	-38.5 (22.2)	-37.5*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
Placebo	N	194	194	170	130	194
	Mean (SD)	78.1 (17.8)	-26.7 (26.0)	-31.6 (26.2)	-32.0 (26.4)	-30.0*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
	Between-group p value	0.58				0.0001

*Adjusted means based on ANCOVA analysis model, with terms for treatment and center and baseline as covariate
Source: Tables 16-17, a21566.pdf, Section 16, pp 56-7

DRUP had expressed concern at the pre-NDA meeting about the potential for unblinding of subjects to their treatment assignment based upon the effect of DRSP/EE on menstrual bleeding patterns. The Division requested the Applicant to provide data concerning the efficacy of DRSP/EE in the first treatment cycle to support a finding of efficacy that would not be potentially confounded by unblinding. The Applicant conducted this analysis, showing that the difference between DRSP/EE and placebo at Cycle 1 in Study 304049 of -8.2 was statistically significant (p=0.0002.

Medical Reviewer's Comments:

- ***A statistically significant difference between treatment arms, favoring DRSP/EE was seen for the primary efficacy variable, change from baseline on the DRSPS score.***
- ***The magnitude of the difference in treatment response between arms at the first cycle suggests that the efficacy results were not attributable to a possible compromise in blinding.***

Table 32 Difference in Change from Baseline at each Treatment Cycle

	DRSPS Mean ± SD (N)			
	DRSP/EE	Placebo	Difference	P-Value
Cycle1 - Baseline	-34 ± 20 (190)	-27 ± 24 (194)	-8 ± 23	0.002
Cycle 2 - Baseline	-37 ± 21 (166)	-32 ± 26 (170)	-5 ± 21	0.036
Cycle 3 - Baseline	39 ± 22 (140)	-32 ± 26 (130)	-7 ± 24	0.023

Source: FDA Statistical Reviewer, based on Applicant's data

10.1.8.4 Secondary Efficacy Endpoint Analysis

Secondary variables were analyzed only using the full analysis set. The secondary endpoints were:

- Change from baseline in the average over three treatment cycles of the three functional impairment items of the DRSPS (Items 22-24 in Table 26).
- Change from baseline in the four CGI scores (interviewer-rated severity of illness, efficacy index and global improvement, and subject-rated global improvement) and number of responders according to the efficacy index
- Change from baseline in the physical and mental summary scales from the SF-36
- Change from baseline in the total score of the first 14 items, the score of medication satisfaction and the score of overall life satisfaction on the Q-LES-Q

- Change from baseline in the PMTS observer and self-rated scales
- Change in body weight: from baseline, between 1st-2nd treatment cycles, between 2nd-3rd treatment cycles and between 1st-3rd treatment cycles

DRSPS Functional Impairment

For the functional impairment items on the DRSPS, the average score over the last five days preceding menses was calculated for each item. On each item, the scale ranged from 1 (not at all) to 6 (extreme), with lower scores indicating less symptomatology. The change from baseline score (averaged over the two run-in cycles) to treatment score (averaged over the three treatment cycles) was compared between treatment arms.

Baseline scores and changes from baseline in each treatment arm for the three functional impairment items are displayed in Table 33 to Table 35. The mean baseline scores on Items 22 (Reduction of Productivity) and 23 (Interference with Social Activities) were similar across groups, while the mean baseline score for Item 24, Interference with Relationships, was significantly greater in the placebo group.

Table 33 Reduction of Productivity Score & Change from Baseline by Treatment Group and Cycle

	Statistic	Baseline average	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 average
DRSP/EE	N	189	189	165	139	189
	Mean (SD)	3.89 (0.92)	-1.84 (1.33)	-1.92 (1.28)	-1.98 (1.31)	-1.98*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
Placebo	N	194	194	170	130	194
	Mean (SD)	3.94 (1.00)	-1.42 (1.49)	-1.74 (1.49)	-1.78 (1.50)	-1.64*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
	Between-group p value	0.58				0.002

*Adjusted means based on ANCOVA analysis model, with terms for treatment and center and baseline as covariate
Source: Tables 25 & 27, a21566.pdf, Section 16, pp 105 & 107

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Table 34 Interference with Social Activities Score & Change from Baseline by Treatment Group and Cycle

	Statistic	Baseline average	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 average
DRSP/EE	N	189	189	165	139	189
	Mean (SD)	3.75 (1.06)	-1.77 (1.43)	-1.88 (1.31)	-1.94 (1.36)	-1.94*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
Placebo	N	194	194	170	130	194
	Mean (SD)	3.83 (1.08)	-1.44 (1.55)	-1.72 (1.54)	-1.71 (1.56)	-1.61*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
	Between-group p value	0.45				0.002

*Adjusted means based on ANCOVA analysis model, with terms for treatment and center and baseline as covariate
Source: Tables 27-28, a21566.pdf, Section 16, pp 107-8

Table 35 Interference with Relationships Score & Change from Baseline by Treatment Group and Cycle

	Statistic	Baseline average	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 average
DRSP/EE	N	189	189	165	139	189
	Mean (SD)	3.95 (1.00)	-1.88 (1.43)	-2.03 (1.29)	-2.05 (1.30)	-2.10*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
Placebo	N	194	194	170	130	194
	Mean (SD)	4.14 (0.94)	-1.51 (1.56)	-1.85 (1.49)	-1.84 (1.52)	-1.68*
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
	Between-group p value	0.03				0.0002

*Adjusted means based on ANCOVA analysis model, with terms for treatment and center and baseline as covariate
Source: Tables 27 & 30, a21566.pdf, Section 16, pp 107 & 110

While both treatment groups displayed statistically significant changes from baseline, the difference seen in the DRSP/EE group was statistically significantly greater than that seen in placebo subjects (p=0.002 for Items 22, [Reduction in Productivity] and 23 [Interference with Social Activities], and p=0.0002 for Item 24 [Interference with Relationships]). The difference from placebo was computed from the ANCOVA model that included baseline value as a covariate (see Table 36).

Table 36 ANCOVA Results on Functional Impairment Items of DRSPS

		DRSP/EE (N =231)	Placebo (N =218)	
Item 22 Reduction of Productivity	n	189	194	
	Adjusted Mean	-1.976	-1.643	
	Difference [1]			-0.334
	P-Value [2]			0.0022
	95% Confidence Limits			-0.546,-0.121
	P-Value [3]			0.0030
Item 23 Interference with Social Activities	n	189	194	
	Adjusted Mean	-1.941	-1.606	
	Difference [1]			-0.335
	P-Value [2]			0.0020
	95% Confidence Limits			-0.546,-0.124
	P-Value [3]			0.0030
Item 24 Interference with Relationships	n	189	194	
	Adjusted Mean	-2.102	-1.682	
	Difference [1]			-0.419
	P-Value [2]			0.0002
	95% Confidence Limits			-0.641,-0.198
	P-Value [3]			0.0003

[1] The difference in adjusted treatment means (i.e. DRSP/EE minus placebo).
[2] P-value from ANCOVA with terms for treatment and center, baseline as covariate.
[3] P-value from rank ANCOVA with terms for treatment, center, baseline as covariate, done if test for normality sig. at .05 lev

Source: Table 27, Section 14, a21566.pdf, p 335

Medical Reviewer's Comments:

- ***A statistically significant difference between DRSP/EE and placebo in change from baseline on the three DRSPS secondary outcome measures was demonstrated, suggesting DRSP/EE-related improvement in social and professional functioning in the late luteal phase.***

CGI Scores

The responses on the CGI parameters were based on subjects' status at treatment Cycle 3 (Visit 7). A last observation carried forward (LOCF) approach was used to impute missing data with scores from the most recent on-treatment data. For the severity of illness parameter, change from baseline was assessed, with baseline data obtained from Visit 4 (beginning of treatment Cycle 1), or earlier if Visit 4 data were missing and this assessment had been done out of the usual window.

Severity of Illness

On the severity of illness parameter, rated from 0 (normal) to 7 (among the most extremely ill patients), baseline scores were comparable between treatment arms, and subjects in each group demonstrated statistically significant improvements from baseline at each treatment cycle ($p<0.0001$). The ANCOVA-estimated mean change from baseline in the DRSP/EE group did not differ significantly from that in the placebo group.

Efficacy Index

The efficacy index parameter was computed by dividing the therapeutic score by the side effect score, each ranging from 1 (lowest) to 4 (highest). Efficacy index scores could range from 0.25 (therapeutic effect unchanged or worse and side effects outweigh therapeutic effect) to 4 (therapeutic effect marked, vast improvement and side effects absent). Efficacy index scores and number of responders were assessed. A responder was defined as one having a therapeutic score of "marked" or "moderate" (3 or 4)

with a side effect score of "none" or "do not significantly interfere with subject's functioning" (1 or 2). The efficacy index score rose in each treatment cycle in each treatment arm, however, the ANCOVA-estimated mean change from baseline in the DRSP/EE group did not differ significantly from that in the placebo group. The responder analysis based on the efficacy index also failed to demonstrate a statistically significant difference in the proportion of responders in each treatment arm.

Global Improvement

Global improvement was rated on a scale of 1 (very much improved) to 7 (very much worse). For both the investigator-rated and subject-rated scores, the mean improvement was greater in the DRSP/EE group, and this level reached statistical significance (p=0.02) in the investigator rating of global improvement.

Medical Reviewer's Comments:

- ***There was evidence of improvement with DRSP/EE treatment only on the CGI investigator-rated global improvement measure.***

SF-36 Scores

The SF-36 baseline was obtained at Visit 4 or Visit 2 if the later data were not available. Eight subscales were computed from the 36 items on the questionnaire; since the responses ranges varied across items, the items were recoded and transformed to a 0-100 scale. From the subscales, two summary scales, mental and physical, were computed and change from baseline to EOT compared across treatment arms.

Baseline scores for both the physical and mental subscales were comparable across treatment arms. Both treatment groups showed statistically significant improvements from baseline to the last treatment cycle (Cycle 3 or EOT for subjects who discontinued early) on both subscales; however, the change was not statistically significantly different between the treatment arms.

Q-LES-Q Scores

The Q-LES-Q was also evaluated for change from baseline (Visit 4) to EOT over three parameters (first 14 items, medication and overall life satisfaction) over the two treatment arms. The first 14 items were rated from 1 (very poor) to 5 (very good). The reported score was then calculated as the percent of the maximum possible score (i.e., actual score/70). Baseline values were comparable between treatment arms, both groups showed significant improvement from baseline to EOT, and this improvement was of borderline statistical significance favoring DRSP/EE (p=0.052).

Satisfaction with medication and overall life satisfaction were each single items, rated on the same 1-5 scale. Medication satisfaction was assessed only at the end of treatment. While the score was slightly higher for the DRSP/EE subjects (3.8 vs. 3.6), it was not statistically significantly different from placebo. For overall life satisfaction, baseline values and change from baseline did not differ significantly between treatment arms, both of which showed statistically significant improvement from baseline.

PMTS Scores

The two PMTS scales were scored differently, but each ranged from 0-36. Change from baseline (Visit 4 preferentially, or Visit 2) to EOT was compared between treatment groups. For both the observer-rated and the self-rated scales, baseline scores were comparable across treatment arms, and both groups showed statistically significant changes from baseline, with the self-rated scale evidencing greater change in each treatment arm than did the observer-rated scale. The difference was statistically significant in favor or DRSP/EE on both scales (p=0.045 for the observer-rated, p=0.002 for the self-rated scale).

Body Weight

Changes in body weight over treatment were compared between treatment arms, with baseline obtained at Visit 4. The baseline weight in the DRSP/EE group was slightly greater than that of placebo subjects, a difference that was of borderline significance (p=0.059). Both groups displayed minor decreases in

weight over treatment, with the only change that was statistically significant being in the DRSP/EE group at cycle 2 (p=0.024), where the mean weight had dropped 0.28 kg from baseline. The differences between treatment arms were not statistically significant at any time.

Medical Reviewer's Comment:

- ***Of five secondary outcome instruments with a total of 14 components, the three DRSPS Functional Impairment items, the two PMTS scales and a single component of the CGI instrument demonstrated a statistically significant benefit to treatment of DRSP/EE over placebo. These instruments measured symptoms and function in the five to seven days preceding menses, as opposed to the SF-36, which generally uses a four-week assessment window.***

10.1.9 Safety

10.1.9.1 Safety Measurements

All participants who received at least one dose of study medication were included in the summaries and listings of safety data (N=249). Adverse events were monitored from run-in Cycle 1 until the final study visit with the exception of pregnancy, which was followed until conclusion. In addition to spontaneous reports, adverse events were elicited at each visit by a general question about any health problems beyond usual PMDD symptoms. Adverse events that began prior to treatment but had maximum intensities of moderate, severe or unknown were categorized as treatment-emergent events. Adverse events were coded according to the Hoecht Adverse Reaction Terminology System (HARTS) dictionary and were summarized by body system and preferred term.

Medical Reviewer's Comment:

- ***The Applicant justifies the decision to consider adverse events of greater than mild intensity that began prior to treatment as treatment emergent by explaining that any escalation of intensity with treatment would not be recorded, as only the maximum intensity was recorded. In addition, stop dates were not always recorded for pre-treatment. A total of 29 such pretreatment adverse events occurred in Study 304049 – 20 of which resolved during treatment (15 among DRSP/EE subjects and four among placebo subjects) and 9 of which had no stop date recorded (seven among DRSP/EE subjects and two among placebo subjects). In the DRSP/EE group, the pretreatment adverse events included nausea (3 cases), menorrhagia (2 cases), and increased triglycerides, decreased libido, and intermenstrual bleeding (1 case each).***

The following safety measurements were evaluated:

- Physical and gynecological examinations and Pap smears
- Vital signs
- Laboratory assessment (hematology, serum chemistries including thyroid [at run-in Cycle 2 only], hepatic and lipid panels, done at run-in Cycle 2, treatment Cycle 2 and EOT, and urinalysis, done at run-in Cycle 2 and EOT
- In addition to adverse events generally, selected cardiovascular (arrhythmia, brady/tachycardia, dizziness, palpitations and syncope) and thromboembolic events were evaluated

Laboratory measures were assessed by summary statistics at baseline (Visit 3), start of treatment Cycle 2 (Visit 5) and EOT (Visit 7). Shifts between categories of low, normal or high from baseline to post-baseline assessments were presented by treatment group. With hyperkalemia being an issue of potential concern, the number and proportion of subjects with serum potassium (K^+) values $\geq$5.5 mEq/L and

≥6.0 mEq/L was tabulated by treatment, and the proportions in each category compared statistically between treatment arms. Change from baseline to Visit 5 in serum K^+, maximum serum K^+, serum creatinine and creatinine clearance was compared by ANCOVA with terms for effects due to treatment and center, and baseline value as a covariate.

Summary statistics were presented for vital signs measurements at each visit and for change from baseline (Visit 4) to Visits 5-7.

10.1.9.1.1 Extent of exposure

Exposure to study drug for the two groups is displayed in Table 37. A full three cycles would entail 72 days of drug exposure, or 84 days of treatment. The difference in the enrolled population and the exposed population is due to the subjects lost to follow-up (13 in the DRSP/EE arm and 14 in the placebo arm).

Table 37 Exposure by Treatment Group

Duration of Treatment (Days) (1)	DRSP/EE (N=231)	Placebo (N=218)
N	218	204
MEAN	68.7	73.8
SD	26.18	21.34
MEDIAN	82	82
MINIMUM	2	2
MAXIMUM	93	126

Source: Table 82, a21566.pdf, Section 16, p 168

Medical Reviewer's Comment:

- ***The shorter mean exposure coupled with identical median exposure values in the DRSP/EE group as compared to the placebo group could be attributable either to greater frequency of DRSP/EE subjects who withdrew early in the trial, or to higher numbers of placebo subjects who had extended exposure. The greater maximum exposure in the placebo group suggests that the latter situation may be an important contributor to the difference in exposure.***

10.1.9.2 Adverse Events

10.1.9.2.1 Serious adverse events

Deaths: There were no deaths in the trial.

Premature termination due to adverse events: Thirty-six DRSP/EE subjects (15.6 %) and nine placebo subjects (4.1%) terminated prematurely from the study because of one or more adverse events. All adverse events leading to withdrawals are listed in Table 38.

Table 38 Treatment Withdrawals due to Adverse Events

Preferred Term	DRSP/EE N=231		Placebo N=218	
	N	%	N	%
Nausea	11	4.8	2	0.9
Intermenstrual bleeding	8	3.5	0	0
Asthenia	7	3.0	1	0.5
Breast pain	4	1.7	0	0
Depression	4	1.7	0	0
Headache	3	1.3	2	0.9
Increased appetite	3	1.3	0	0
Menorrhagia	3	1.3	0	0
Abdomen enlarged	2	0.9	1	0.5
Acne	2	0.9	1	0.5
Nervousness	2	0.9	1	0.5
Breast engorgement	2	0.9	0	0
Constipation	2	0.9	0	0
Emotional lability	2	0.9	0	0
Insomnia	2	0.9	0	0
Menstrual disorder	2	0.9	0	0
Palpitation	2	0.9	0	0
Weight gain	2	0.9	0	0
Vomiting	2	0.9	0	0
Abdominal pain	1	0.4	0	0
Anorexia	1	0.4	0	0
Bleeding time increased	1	0.4	0	0
CNS disorder*	1	0.4	0	0
Dysmenorrhea	1	0.4	0	0
Hot flashes	1	0.4	0	0
Hyperlipemia	1	0.4	0	0
Incoordination	1	0.4	0	0
Migraine	1	0.4	0	0
Pain	1	0.4	0	0
Pain in extremity**	1	0.4	0	0
Psychosis***	1	0.4	0	0
Sweating increased	1	0.4	0	0
Thrombocytopenia	1	0.4	0	0
Anxiety	0	0	2	0.9
Apathy	0	0	1	0.5
Chills	0	0	1	0.5
Eye pain	0	0	1	0.5
Hypertension	0	0	1	0.5
Skin disorder	0	0	1	0.5

Number of events exceed number of withdrawals, because some subjects experienced multiple events
*A single subject reported decreased cognitive ability, decreased motor skills (incoordination) and emotional lability
**Doppler showed no evidence DVT
***Subject reported continuous paranoia with first dose; recovered without additional treatment after DRSP/EE discontinued on day 3
Source: Text Table 35, a21566.pdf, p 119

Medical Reviewer's Comment:

- ***The most common adverse events leading to differential withdrawal in the DRSP/EE and placebo groups tend to be side effects commonly associated with oral contraceptives, including intermenstrual bleeding, breast tenderness and mood changes. They do not suggest a safety profile of greater concern than any other oral contraceptive.***

Serious adverse events: There were three DRSP/EE and one placebo group subjects who experienced serious adverse events during the treatment period, listed in Table 39; the overall rate was 1.3% in the DRSP/EE group and 0.5% in the placebo group.

Table 39 Serious Adverse Events during Treatment

SAE (Subject #)	Treatment	Causality	Timing	Intensity	Resolution
Lower abdominal pain (incarcerated incisional hernia) (510008)	DRSP/EE	Unrelated	5 weeks after first dose	Moderate	Recovered following surgery
Lower back bone spurs (190004)	DRSP/EE	Unrelated	5 weeks after first dose	Severe	Recovered following surgery
Severe dysplasia on Pap (HSIL) (560002)	DRSP/EE	Possibly related	12 weeks after first dose (Visit 7)	Severe	Unknown – colposcopic dx and LEEP pathology unknown
Appendicitis (380066)	Placebo	Unrelated	8 weeks after first dose	Severe	Recovered following surgery

Source: Table 91, a21566.pdf, Section 16, p 219

Medical Reviewer's Comment:

- ***In the reviewer's opinion, no SAEs were plausibly associated with DRSP/EE. The subject with HSIL at Visit 7 had previously had a Pap result of LSIL at Visit 3 (run-in 2).***

10.1.9.2.2 Frequent adverse events

At least one adverse event was reported by 194 (80%) and 140 (64%) of the DRSP/EE and placebo subjects, respectively. Events occurring at ≥ 5% frequency only in the DRSP/EE group were:

- Intermenstrual bleeding
- Asthenia
- Abdominal pain

Overall adverse events occurring with frequency ≥ 2% in either group are reported in Table 40. Body systems with increased frequency of clusters of adverse events in the DRSP/EE group as compared to placebo were:

- Nervous system/CNS, primarily due to increased rates of depression and emotional lability (7.8% in DRSP/EE vs. 2.3% in placebo)
- Skin/breast, primarily due to increased rates of breast engorgement, enlargement and pain (16% in DRSP/EE vs. 6% in placebo)
- Urogenital/female genitalia/menstrual, primarily due to increased rates of intermenstrual bleeding, menorrhagia and vaginal hemorrhage (31.2% in DRSP/EE vs. 6% in placebo)

Table 40 Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects

Adverse Event	DRSP/EE N=231		Placebo N=218	
	N	%	N	%
Intermenstrual bleeding	60	26.0	10	4.6
Headache	45	19.5	44	20.2
Nausea	43	18.6	11	5.1
Breast pain	31	13.4	11	5.1
URI	23	10.0	24	11.0
Asthenia	19	8.2	8	3.7
Abdominal pain	12	5.2	6	2.8
Libido decreased	11	4.8	3	1.4
Pap smear suspicious	11	4.8	7	3.2
Emotional lability	10	4.3	3	1.4
Menorrhagia	10	4.3	3	1.4
Sinusitis	9	3.9	11	5.1
Depression	8	3.5	2	0.9
Pain in extremity	8	3.5	1	0.5
Weight gain	8	3.5	8	3.4
Increased appetite	7	3.0	0	0
Migraine	7	3.0	3	1.4
Vaginal moniliasis	7	3.0	7	3.2
Abdomen enlarged	6	2.6	5	2.3
Acne	6	2.6	7	3.2
Diarrhea	6	2.6	4	1.8
Hyperlipemia	6	2.6	1	0.5
Menstrual disorder	6	2.6	5	2.3
Vaginitis	6	2.6	6	2.8
Accidental injury	5	2.2	5	2.3
Breast engorgement	5	2.2	2	0.9
Nervousness	5	2.2	2	0.9
Flu syndrome	2	0.9	5	2.3
Bronchitis	1	0.4	5	2.3

Source: Text Table 34, a21566.pdf, p 114

Medical Reviewer's Comment:

- ***In addition to the hyperlipemia reported, three DRSP/EE and one placebo subjects experienced hypercholesterolemia, bringing the rates of elevated lipids to 3.9 and 0.9%, respectively.***

The frequency of adverse events considered by the investigator to be drug-related was higher in the DRSP/EE group (51% vs. 30% in the placebo group). Among the three clusters of symptoms that were more common in DRSP/EE subjects, higher proportions of the mood disorders occurring in the DRSP/EE than in the placebo group were considered drug-related by the investigators (17 of 18 in DRSP/EE subjects and one of five in placebo subjects), while similar proportions of breast pain disorders and menstrual disorders were considered drug-related in each group (33 of 37 breast pain disorders in DRSP/EE subjects and 11 of 13 in placebo subjects; 69 of 72 menstrual disorders in DRSP/EE subjects and 12 of 13 in placebo subjects).

Medical Reviewer's Comment:

- ***The three clusters of adverse events seen with increased frequency in the DRSP/EE group as compared to placebo (mood, breast and menstrual disorders) represent adverse events commonly reported with oral contraceptives and discussed in the labeling for Yasmin.***

10.1.9.3 Cardiovascular and Thromboembolic Events

Due to the potential potassium-sparing effect of drospirenone, the Applicant specifically surveyed adverse events that might be associated with hyperkalemia (arrhythmia, bradycardia, dizziness, palpitation, syncope and tachycardia). No subjects experienced bradycardia or tachycardia as an adverse event. A total of seven (3.0%) of DRSP/EE subjects and three (1.4%) of placebo subjects reported one of these adverse events (Table 41). (See Section 10.1.9.4 for further discussion of laboratory abnormalities.)

Table 41 Cardiovascular Events by Treatment Group

Cardiovascular Events	DRSP/EE N=231	Placebo N=218
Arrhythmia	1(0.4%)	0(0.0%)
Bradycardia	0(0.0%)	0(0.0%)
Dizziness	4(1.7%)	2(0.9%)
Palpitation	2(0.9%)	0(0.0%)
Syncope	0(0.0%)	1(0.5%)
Tachycardia	0(0.0%)	0(0.0%)

Source: Table 88, a21566.pdf, Section 15, p 216

Subjects experiencing one of these events had the following potassium levels (normal range 3.4-5.4 mEq/L):

- #30044 (DRSP/EE, dizziness): run-in – 4.9, cycle 2 – 4.5, EOT – 5.3 mEq/L
- #180056 (DRSP/EE, dizziness): run-in – 3.9, cycle 2 – 4.0, EOT – 3.6 mEq/L
- #500091 (DRSP/EE, dizziness): run-in – 4.4, cycle 2 – 4.4, EOT – 4.4 mEq/L
- #840066 (DRSP/EE, dizziness): run-in – 4.4, cycle 2 – 4.2, EOT – 4.9 mEq/L
- #270010 (DRSP/EE, arrhythmia): run-in – 4.1, cycle 2 – 4.0, EOT – 4.3 mEq/L
- #260001 (DRSP/EE, palpitation): run-in – 3.6, EOT – 4.0 mEq/L (discontinued due to adverse events after 1 treatment cycle)
- #840002 (DRSP/EE, palpitation): run-in – 3.9, EOT – 4.5 mEq/L (discontinued due to adverse events midway through second treatment cycle)
- #270011 (placebo, dizziness): run-in – 4.2, cycle 2 – 4.7, EOT – 4.2 mEq/L
- # 470079 (placebo, dizziness): run-in – 3.9, cycle 2 – 3.6, EOT – 4.5 mEq/L
- #520030 (placebo, syncope): run-in – 4.1, EOT – 4.6 mEq/L

No subject in either treatment group experienced a thromboembolic event.

Medical Reviewer's Comment:

- ***At least one additional DRSP/EE and one placebo subject experienced vertigo, which might represent a cardiovascular event.***
- ***Overall, the reviewer does not believe that the antimineralocorticoid properties of DRSP are related to the excess of these cardiovascular adverse events in subjects taking DRSP/EE.***
- ***Eight DRSP/EE subjects and one placebo subjects experienced the adverse event "pain in extremity." Doppler evaluation was obtained in one DRSP/EE subject and was negative for DVT. The remaining events comprised wrist pain, knee pain, leg cramps and bilateral leg pain and no further evaluation was reported.***

10.1.9.4 Laboratory Values and Urinalysis

The serum chemistry, hematology, and urinalysis test results were reviewed. All laboratory analyses were performed by a central laboratory, Covance.

Hematology

Three subjects had adverse events reported relating to hematologic values, none of which were considered clinically relevant by the investigator:

- #20036 (DRSP/EE) – no platelet value available at run-in Cycle 2 or repeat done four weeks later, due to microclots in the samples. On the second day she received study drug, the investigator diagnosed her condition as thrombocytopenia based on the laboratory report, and she was immediately discontinued early, due to the adverse event of thrombocytopenia.
- #180081 (DRSP/EE) had a run-in hemoglobin of 13 g/dl (reference range 11.6-16.4), and study medication was discontinued due to fatigue after seven weeks of treatment. She prematurely withdrew from the study approximately six weeks later, with the fatigue unresolved, and her EOT hemoglobin value was 9.3 g/dl.
- #30026 (placebo) had a low hemoglobin value of 11.3 g/dl at run-in, which decreased to 10.7 at the Treatment Cycle 2 visit. She discontinued prematurely due to consent withdrawal and her EOT visit the following day showed normal-range hemoglobin of 11.6 g/dl.

Medical Reviewer's Comments:

- ***The attribution of low hemoglobin in Subject #180081 is unclear. It might be due to effects of DRSP/EE on bleeding profile, but this subject had no past history of intermenstrual bleeding, and did not report any menstrual disorders as adverse events during her participation in the trial.***

Selected mean and median values at baseline, treatment Cycle 2 and at Visit 7 or at the time of early withdrawal are presented in Table 42. Shift tables showed that fewer than 3% in either treatment arm shifted from normal or high hematocrit or hemoglobin values at baseline to low values over the course of treatment, and the proportion shifting to low values was greater in the placebo group. No subject shifted into the low value category for platelets, and the proportion shifting from low or normal values to high values was greater in the placebo group.

Table 42 Mean (SD) and Median Hematology Safety Variables

Lab Test		DRSP/EE N=231			Placebo N=218		
		N	Mean (SD)	Median	N	Mean (SD)	Median
Hematocrit (%)	Baseline	225	41.2 (3.1)	41.0	213	40.8 (3.3)	41.0
	Tx Cycle 2	168	40.4 (3.0)	40.0	179	40.1 (3.1)	40.0
	EOT	207	40.4 (2.6)	41.0	201	40.2 (3.1)	40.0
Hemoglobin (g/L)	Baseline	228	13.6 (1.0)	13.6	214	13.5 (1.1)	13.5
	Tx Cycle 2	170	13.4 (1.0)	13.4	181	13.3 (1.1)	13.3
	EOT	207	13.5 (1.0)	13.5	201	13.5 (1.1)	13.5
Platelets (10^9/L)	Baseline	225	274.8 (54.0)	267.0	208	279.9 (66.6)	270.0
	Tx Cycle 2	167	270.1 (65.4)	263.0	180	275.5 (60.3)	274.0
	EOT	206	281.2 (62.3)	278.0	200	280.9 (61.4)	277.5

EOT = Visit 7 or end of treatment visit if subject terminated prematurely
Source: Table 94, a21566.pdf, Section 16, pp 454-463

Medical Reviewer's Comments:

- ***Changes in hematologic variables were minimal. The minimum and maximum values seen with treatment for hemoglobin and hematocrit were more extreme in the placebo group.***

Chemistry

General Chemistry

A total of 16 DRSP/EE subjects and six placebo subjects had abnormal postbaseline chemistry values that were considered to be clinically relevant. Among the 16 DRSP/EE subjects, there were 14 lipid abnormalities (seven of which were considered adverse events), two glucose abnormalities and one involving AST/ALT and calcium (none of which were considered adverse events). (Some subjects experienced clinically relevant abnormalities in more than one parameter.) Three placebo subjects had lipid abnormalities; in one case, the elevation in cholesterol was considered an adverse event. The remaining clinically relevant abnormalities in placebo subjects involved AST/ALT, alkaline phosphatase/ALT and calcium, in one subject each. An additional DRSP/EE subject and two placebo subjects had chemistry values that were reported as adverse events, but were not considered clinically relevant (elevated cholesterol in the DRPS/EE subject; low glucose and elevated triglycerides in placebo subjects).

Selected chemistry values at baseline and over the course of treatment are displayed in Table 43.

Table 43 Mean (SD) Chemistry Safety Variables

Lab Test		DRSP/EE N=136		Placebo N=138	
		N	Mean (SD)	N	Mean (SD)
Creatinine (mg/dl)	Baseline	231	0.73 (0.12)	214	0.72 (0.11)
	Cycle 2	174	0.76 (0.13)	183	0.71 (0.13)
	EOT	210	0.73 (0.12)	204	0.71 (0.12)
Potassium (mEq/L)	Baseline	231	4.28 (0.40)	214	4.23 (0.36)
	Cycle 2	173	4.34 (0.42)	182	4.26 (0.38)
	EOT	209	4.29 (0.38)	204	4.28 (0.39)
Glucose (mg/dl)	Baseline	231	88.3 (10.3)	214	87.2 (9.0)
	Cycle 2	173	88.4 (11.6)	183	88.5 (14.5)
	EOT	209	88.9 (11.6)	204	87.4 (11.9)
AST (U/L)	Baseline	230	20.2 (6.0)	214	20.3 (6.6)
	Cycle 2	172	18.1 (4.8)	182	19.6 (6.5)
	EOT	208	19.7 (6.1)	204	20.2 (6.6)
ALT (U/L)	Baseline	231	17.7 (10.1)	214	18.1 (11.2)
	Cycle 2	172	15.2 (5.8)	182	16.9 (9.6)
	EOT	208	16.9 (10.7)	204	17.5 (9.5)
Alk Phos (U/L)	Baseline	231	62.9 (18.3)	213	60.5 (14.8)
	Cycle 2	174	52.7 (16.2)	182	59.2 (16.0)
	EOT	210	56.9 (17.1)	204	59.1 (16.3)
Total Bili (mg/dl)	Baseline	231	0.49 (0.24)	213	0.48 (0.22)
	Cycle 2	173	0.41 (0.21)	183	0.47 (0.21)
	EOT	209	0.44 (0.20)	204	0.49 (0.23)
Total Cholesterol (mg/dl)	Baseline	231	182.1 (34.4)	214	180.9 (31.8)
	Cycle 2	174	186.0 (33.5)	183	174.0 (31.5)
	EOT	210	195.9 (34.7)	204	178.6 (33.0)
Triglycerides (mg/dl)	Baseline	231	102.8 (57.8)	213	100.8 (52.0)
	Cycle 2	174	150.5 (299.5)	183	100.0 (64.9)
	EOT	210	129.5 (72.9)	204	102.2 (53.8)

EOT = Visit 7 or end of treatment visit if subject terminated prematurely
Source: Table 97, a21566.pdf, Section 16, p 484-500

Medical Reviewer's Comment:

- ***The Cycle 2 triglyceride value for the DRSP/EE group is inflated by an erroneous maximum value of 3994 mg/dl. The laboratory report with this value notes that the value was dismissed and further evaluation needed.***

Creatinine and Creatinine Clearance

A single placebo subject experienced an elevated creatinine level (1.4 mg/dl, normal range 0.4 – 1.1 mg/dl), which occurred at treatment Cycle 2 and resolved. However, the difference between groups in change in creatinine from baseline to treatment Cycle 2 was statistically significant (DRSP/EE increased by 0.02 mg/dl, while placebo decreased by 0.01 mg/dl, p=0.0017). The difference was not statistically significant at the EOT visit.

Creatinine clearance was calculated using the standard formula for females. At baseline, four DRSP/EE and six placebo subjects showed mild renal impairment (creatinine clearance >50 and ≤80 ml/min). Mean and maximum on-treatment potassium levels were lower in these subjects with mild renal impairment as compared to subjects with normal creatinine clearance. An additional nine DRSP/EE subjects and ten placebo subjects experienced mild renal impairment on treatment. No subjects had moderate or severe impairment at any assessment. There was a statistically significant difference in change in creatinine clearance from baseline to treatment Cycle 2 (DRSP/EE decreased by 2.05 ml/min, while placebo increased by 2.94 ml/min, p=0.046). The difference was not statistically significant at the EOT visit.

Potassium

Particular precautions were taken in obtaining serum potassium measurements, to avoid potential falsely elevated values. These included avoidance of tourniquet use, and visual and photometric assessment for hemolysis of the sample following centrifugation. Hemolyzed specimens were discarded and resampling was done.

Potassium levels changed minimally over treatment, showing a median change of 0 and a maximum mean change of 0.05 mEq/L in both groups at various on-treatment assessments. Differences between treatment arms in change from baseline were not statistically significant. The maximal potassium value on treatment was 6.0 mEq/L, occurring in a single subject in the DRSP/EE group, during treatment Cycle 2. Table 44 lists the four DRSP/EE and one placebo subjects had potassium levels above 5.4 during treatment; elevations in the active treatment subjects all occurred at treatment Cycle 2 and resolved by the EOT visit. Of these subjects, one of the DRSP/EE subjects had an on-treatment creatinine clearance value indicating mild renal impairment. None of the five subjects with these elevations in potassium experienced any of the selected cardiovascular events surveyed (see Section 10.1.9.3). None was taking any concomitant medications that might affect serum potassium. The only value considered clinically relevant was in Subject #380122; however, it returned to 4.4 mEq/L four days later without medication withdrawal.

Table 44 Listing of Subjects with Elevated Postbaseline Potassium Levels

Treatment	Subject #	Baseline Value (mEq/L)	Cycle 2 Value (mEq/L)	EOT Value (mEq/L)	Renal Function at high K^+ value
DRSP/EE	200056	4.3	**5.5**	4.5	Mild impairment
	380122	4.4	**6.0**	4.7	Normal
	470094*	5.4	4.5	4.4	Normal
	510008	4.3	**5.7**	5.1	Normal
Placebo	840058	5.4	4.8	**5.6**	Normal

*Subject #470094 actually had her elevated value drawn pre-dosing at Visit 4; however, the protocol counts all samples on the same day as dosing as post-baseline values, so she is included in this table.
Source: a21566.pdf, pp 135-6

The difference between treatment groups in the proportion of subjects with potassium levels ≥ 5.5 mg/dl was not statistically significant (1.9% of DRSP/EE subjects vs. 0.5% of placebo subjects). Table 45 displays the percent of subjects who experienced transitions in potassium levels with treatment. A greater proportion of DRSP/EE subjects than placebo subjects shifted from normal baseline potassium values to high at Cycle 2 (1.7% vs. 0%), but by EOT, no DRSP/EE subject and one placebo subject experienced high values.

Table 45 Transitions in Potassium Values with Treatment

Parameter	Treatment Cycle	Treatment Group	Baseline Value (%)	Low (%)	Normal (%)	High (%)	Total (%)
Potassium	Cycle 2	DRSP/EE	Low (%)	0	0	0	0
			Normal (%)	0	169 (97.7)	3 (1.7)	172 (99.4)
			High (%)	0	1 (0.6)	0	1 (0.6)
			Total (%)	0	170 (98.3)	3 (1.7)	173 (100)
		Placebo	Low (%)	0	1 (0.6)	0	1 (0.6)
			Normal (%)	2 (1.1)	177 (98.3)	0	179 (99.4)
			High (%)	0	0	0	0
			Total (%)	2 (1.1)	178 (98.9)	0	180 (100)
	EOT	DRSP/EE	Low (%)	0	0	0	0
			Normal (%)	0	208 (99.5)	0	208 (99.5)
			High (%)	0	1 (0.5)	0	1 (0.5)
			Total (%)	0	209 (100)	0	209 (100)
		Placebo	Low (%)	0	1 (0.5)	0	1 (0.5)
			Normal (%)	0	198 (99.0)	1 (0.5)	199 (99.0)
			High (%)	0	0	0	0
			Total (%)	0	199 (99.5)	1 (0.5)	200 (100)

Source: Table 99, a21566.pdf, p 543

Lipids

Fourteen DRSP/EE subjects and three placebo subjects had lipid values that were outside the normal range and judged to be clinically relevant. Eleven DRSP/EE subjects had elevated triglyceride values on treatment; however, only one of these subjects had a normal baseline value. Of the remaining ten, nine experienced further rises in triglycerides during therapy, and one decreased from the elevated baseline. A single placebo subject experienced a clinically relevant elevated triglyceride level, rising from a normal baseline. Five DRSP/EE subjects experienced clinically relevant elevated total cholesterol levels – two of these followed normal baseline values, one represented an increase over an elevated baseline, and two were actually decreased from elevated baseline levels. A single placebo subject had an increase from a normal baseline that was judged to be clinically relevant. One DRSP/EE and one placebo subject had normal baseline LDL values that rose to clinically relevant abnormal levels during treatment. An additional DRSP/EE subject had elevated triglycerides reported as an adverse event; she discontinued prematurely due to an unrelated adverse event. One placebo subject with elevated triglycerides at baseline developed further increases on treatment, which was reported as an adverse event. By the EOT visit, 6.7% of DRSP/EE subjects had shifted from normal baseline values to high values on total cholesterol, as compared to 4.0% of placebo subjects. For triglycerides, the comparable figures for subjects who had shifted from normal baseline values to high values by the EOT visit were 14.3% of DRSP/EE subjects and 6.5% of placebo subjects. No DRSP/EE subjects with normal baseline HDL levels shifted to low levels over treatment. Shifts were similar for LDL cholesterol with 2.9% of

DRSP/EE subjects and 2.0% of placebo subjects who had normal baseline levels shifting to high values by EOT.

Medical Reviewer's Comment:

- ***There was no evidence of significant hyperkalemia with DRSP/EE treatment, and, based on a small number of subjects, no evidence that mild renal impairment had an adverse impact on potassium levels during treatment.***
- ***Liver enzymes were typically lower on treatment in the DRSP/EE group and showed a greater mean and median decrease from baseline over treatment.***
- ***The mean cholesterol and triglyceride values during treatment were greater in the DRSP/EE group than in the placebo group, despite similar baseline values. No tests of significance were provided. The DRSP/EE group also showed increases from baseline to treatment Cycle 2 and EOT in total cholesterol and triglycerides, while the placebo group decreased. Greater percentages of the DRSP/EE group as compared to the placebo group experienced transitions from normal to high values on total cholesterol and triglycerides over treatment.***
- ***Other laboratory values did not show notable change from baseline or difference between treatment groups.***

Urinalysis

Two placebo subjects had clinically relevant urinalysis findings on treatment that were attributed to urinary tract infections. No other relevant changes in urinalysis parameters were noted on treatment.

10.1.9.5 Pregnancies

One subject in each group became pregnant during the study. The DRSP/EE pregnancy (#160021) was conceived approximately three weeks after the last dose of study medication, and four days following early withdrawal from the trial. A normal pregnancy ensued, with vaginal delivery of a healthy male. The placebo pregnancy (#30017) was detected at Day 84, at the EOT visit, three days after completing study medication. Eight months later, following a normal pregnancy, a healthy child was delivered vaginally. Both subjects reported using condoms during the trial.

Medical Reviewer's Comment:

- ***No pregnancies appear to have occurred during DRSP/EE administration.***

10.1.9.6 Vital Signs

Blood pressure, pulse and temperature were assessed at each study visit. Mean values for blood pressure and pulse at each treatment cycle are presented in Table 46. There was a trend toward slightly greater increases in blood pressure with DRSP/EE than with placebo. Only minimal mean and median changes from baseline in blood pressure were seen in either group (Systolic blood pressure decreased by 1.1 mm Hg at EOT in the DRSP/EE group, and by 1.3 mm Hg in the placebo group; diastolic blood pressure increased by 0.6 mm Hg at EOT in the DRSP/EE group, and decreased by 0.5 mm Hg in the placebo group. Mean temperature was the same in each group at baseline, and changed minimally at each treatment cycle in both groups.

Table 46 Mean (SD) Blood Pressure and Pulse by Treatment Group and Time

Vital Sign	Treatment	Baseline	Cycle 2	Cycle 3	EOT
Systolic BP (mm Hg)	N	231	186	162	214
	DRSP/EE	111.6 (12.2)	109.9 (10.8)	112.0 (10.9)	110.4 (11.2)
	N	218	187	170	207
	Placebo	111.4 (10.7)	110.1 (10.5)	111.0 (11.4)	110.2 (10.7)
Diastolic BP (mm Hg)	N	231	186	162	214
	DRSP/EE	71.3 (8.1)	71.2 (8.2)	71.9 (8.1)	71.8 (8.6)
	N	218	186	170	207
	Placebo	71.0 (8.1)	70.8 (7.4)	70.4 (8.2)	70.6 (7.8)
Pulse (BPM)	N	231	186	161	214
	DRSP/EE	71.4 (9.0)	70.6 (9.0)	71.9 (10.0)	72.6 (9.7)
	N	218	187	170	207
	Placebo	70.4 (9.2)	70.2 (9.6)	71.4 (9.0)	69.9 (9.2)

Source: Table 113, a21566.pdf, Section 16, p 384-6

One subject in each group reported mild hypertension as an adverse event over the course of treatment, with the placebo subject terminating prematurely due to this event. Both subjects had resolution of the event.

Medical Reviewer's Comment:

- ***The differences between treatment arms in blood pressure and pulse at EOT are not believed by the reviewer to be clinically significant. Only descriptive statistics were provided.***

10.1.9.7 Physical and Gynecological Examinations

Physical and gynecological exams, including Pap smear, were performed at run-in Cycle 2 and the EOT visits. Eight DRSP/EE subjects and nine placebo subjects had changes on physical exam that were judged by the Applicant to be clinically significant.

Similarly, four DRSP/EE subjects and six placebo subjects had changes on gynecological exam judged to be clinically significant by the Applicant. These ranged from vaginal infections to cervical ectropion to a small ovarian cyst (placebo subject).

Twenty-six DRSP/EE subjects (11.3%) and 21 placebo subjects (9.6%) had abnormal Pap smear results subsequent to the baseline assessment.

Medical Reviewer's Comment:

- ***Changes on physical exam in DRSP/EE subjects judged by the reviewer to be potentially relevant were:***
  - ***#110001 – developed left breast density; ultrasound found no solid or cystic mass; resolved***
  - ***#130062 – bilateral fibrocystic breast tissue became tender; discontinued prematurely due to adverse events; outcome unknown***
  - ***#220001 – increased acne; discontinued prematurely due to this and other adverse events***
- ***No changes on gynecological exam were judged by the reviewer to be potentially relevant.***
- ***No concise listing of subjects with abnormal post-baseline Pap smears is provided. It is reported that 64% of DRSP/EE subjects and 76% of placebo subjects who had abnormal***

Pap smears had the results judged as clinically insignificant by the investigators, but no basis for this decision is given.

10.1.10 Reviewer's assessment of efficacy and safety

Efficacy

In the primary efficacy analysis, superiority of DRSP/EE to placebo in reduction of PMDD symptoms as measured by the first 21 items of the DRSPS from baseline to the average over three treatment cycles was evaluated using an ANCOVA model with treatment and center as factors and baseline as a covariate. The principal analysis, relied upon by the reviewer, utilized the modified ITT population.

The ANCOVA results demonstrated a statistically significant difference between DRSP/EE and placebo groups in the adjusted mean change from baseline averaged over the three treatment cycles, with the improvement in the DRSP/EE group 7.5 points greater (95% confidence limits 3.8 to 11.2) than that experienced by placebo subjects (p=0.0001). Results were very similar, with the same p-values, when analyzed using the per protocol population.

DRUP had expressed concern at the pre-NDA meeting about the potential for unblinding of subjects to their treatment assignment based upon the effect of DRSP/EE on menstrual bleeding patterns. The Division requested the Applicant to provide data concerning the efficacy of DRSP/EE in the first treatment cycle to support a finding of efficacy that would not be potentially confounded by unblinding. The Applicant conducted this analysis, showing that the difference between DRSP/EE and placebo at Cycle 1 in Study 304049 of -8.2 was statistically significant (p=0.0002). The magnitude of the difference in treatment response between arms at the first cycle suggests that the efficacy results were not attributable to a possible compromise in blinding.

Six additional outcome measures (functional items from the DRSPS, the CGI, the SF-36, the Q-LES-Q, the PMTS and change in body weight) were assessed as secondary endpoints; since several had multiple components, a total of 17 secondary endpoints were evaluated. Of these, statistically significant differences between DRSP/EE and placebo groups were demonstrated for:

- Change from baseline in the average over three treatment cycles of the three functional impairment items of the DRSPS (Items 22-24 in Table 26).
- Change from baseline in one of four CGI scores (interviewer-rated global improvement).
- Change from baseline in the PMTS observer and self-rated scales.

The measures on which significant change was demonstrated for DRSP/EE treatment tended to assess symptoms and function over the week preceding menses, rather than over a longer time period, as does the SF-36.

The Division had requested that the Applicant show that changes in symptomatology occurring with treatment were of clinical benefit to subjects, by providing a value for the minimally important clinical difference (MICD) between the responses of the treatment and placebo groups and by describing the method by which the MICD was determined. Although the Applicant did not provide an actual value for MICD, the estimated effect size, calculated by dividing the mean difference in response between treatment and placebo groups by the corresponding standard deviation (SD), was suggested as a proxy for MICD. By convention[1], effect sizes of 0.2, 0.5 and 0.8 SD units represent small, medium and large treatment effects. The effect size for DRSP/EE in Study 304049, which is shown graphically in Figure 2, appears to be about 0.4, with 95% CI ranging from about 0.2 - 0.6, falling in the range of a small – medium effect size, fairly similar to effect sizes calculated from pooled published studies on SSRIs.

The benefit of DRSP/EE treatment can also be assessed by comparison with the approved SSRI treatments for PMDD. A number of NDAs have been submitted seeking approval for SSRI treatment of PMDD, either on a continuous basis, or using intermittent dosing during the luteal phase. The FDA reviews of submissions relating to the three approved drugs (fluoxetine, approved for continuous use on 7/6/00 and for luteal phase use on 6/12/02; sertraline, approved for continuous and luteal phase dosing on 5/16/02; and paroxetine, approved for continuous use on 8/27/03; and for luteal phase dosing (approved on January 27, 2004) were utilized in order to compare the treatment effects noted with the SSRIs with that observed for DRSP/EE.

The most relevant comparison to results obtained with DRSP/EE is with the fluoxetine luteal phase trial, which used the identical outcome measure (the DRSPS, first 21 items), over the same treatment period. On-treatment scores were averaged over the three treatment cycles, as in the DRSP/EE trial. The placebo response is equivalent to that seen in the DRSP/EE trial, as are the study drug responses, both in terms of percent change and actual change from baseline. The recommendation concerning fluoxetine was for an approvable action pending acceptable labeling. Comparative results from this trial and from Study 304049 are shown in Table 47.

The placebo responses on change from baseline were -23 for fluoxetine, vs. -30 for DRSP/EE in Study 304049. The study drug responses were -28 to -31 depending on fluoxetine dose, compared to -37.5 for DRSP/EE in Study 304049. Despite the higher placebo response in the DRSP/EE trials, the magnitude of the difference between study drug and placebo in change from baseline in DRSPS 21 scores was similar (5 to 8 for fluoxetine, 7.5 for DRSP/EE). This treatment effect was judged to provide adequate evidence of efficacy for the SSRI, supporting a recommendation for approvability.

Table 47 Comparative Results from SSRI Trials and DRSP/EE Trial

Drug/Trial/Exposure	Outcome Measure	
NDA 18-936, S-067 (Fluoxetine luteal phase dose)		
Treatment Group (N)	**% change from baseline in DRSPS 21, averaged over 3 treatment cycles**	**Actual change from baseline in DRSPS 21, averaged over 3 treatment cycles**
Placebo (88)	-30%	-23
Fluoxetine 10 mg (86)	-35%	-28 (NS)
Fluoxetine 20 mg (86)	-38%	-31 (p=0.005)
NDA 21-873, DRSP/EE, Study 304149		
Placebo (190)	-38% (30/78.1 Table 18)	-30
DRSP/EE (194)	-48% (37.5/77.4)	-37.5 (p=0.0001)

Source: Review of NDA 18-936, S-067 by Dr. Thomas Laughren, DNDP, December 15, 2001

In summary, this study demonstrated a statistically significant advantage of DRSP/EE over placebo in treatment of PMDD symptoms as measured by the first 21 items of the DRSPS. This difference appears at the first cycle of treatment, reducing the possibility that unblinding due to drug effects on bleeding patterns may account for the difference. Statistically significant differences were also demonstrated on several relevant secondary endpoints, particularly those concerned with changes in symptoms and function in the week prior to menses. Clinical relevance, proposed by the Applicant to be measured by calculated effect size, appears to be demonstrated with an effect size similar to that seen in a number of published studies of SSRIs used to treat PMDD. In addition, the actual responses, both in terms of actual change and percent change from baseline in the first 21 items of the DRSPS, are equivalent to those seen for the approved product, fluoxetine, with luteal phase dosing.

The FDA statistician reviewed the two pivotal phase 3 studies and concluded that Study 304049 showed statistically significant superiority of DRSP/EE to placebo in change from baseline in DRSPS scores ($p < 0.005$).

This reviewer concurs that the results of Study 304049 provide evidence of the efficacy of DRSP/EE in treating symptoms of PMDD.

Safety:

There were no deaths and few serious adverse events in this study. Discontinuations due to adverse events were more frequent in the DRSP/EE group, and were most often attributable to adverse events associated with oral contraceptive use, such as menstrual disorders, breast pain and mood disorders. The overall frequency of adverse events was higher in the DRSP/EE group (80%) than in the placebo group (64%), and similarly, showed a disproportionate number of menstrual, breast and mood disorders occurring in the DRSP/EE group. Special attention was paid to issues of potential concern, including cardiovascular adverse events that might arise as sequelae to hyperkalemia due to DRSP's antimineralocorticoid properties, and VTEs, which are associated with oral contraceptive use. Although nonserious cardiovascular events (total reports of arrhythmia, dizziness, palpitations, and syncope) occurred with over twice the frequency in the DRSP/EE group (3.0% vs. 1.4% in the placebo group), in no cases was there any associated potassium level indicating hyperkalemia. The majority of the DRSP/EE cardiovascular events were dizziness and palpitations. Thus, there does not appear to be a serious cardiovascular safety signal associated with use of DRSP/EE. There were no VTEs in the trial.

Evaluation of laboratory assessments showed that a small but increased percent of DRSP/EE subjects as compared to placebo subjects had increases in potassium level to outside of the normal range over the course of treatment. However, these elevated potassium levels were not associated with cardiovascular sequelae in any case, and tended to resolve without discontinuation of DRSP/EE. No potassium values above the normal range were reported at the end of treatment visit. The overall mean change in potassium level with treatment was minimal and similar to that experienced in the placebo group. There did not appear to be an increased risk of renal impairment with DRSP/EE use. As is recognized for oral contraceptives generally, DRSP/EE had an adverse impact on lipids, primarily affecting triglycerides and total cholesterol, with almost double the percent of DRSP/EE as opposed to placebo subjects shifting from normal baseline values to high values on treatment.

Vital signs data show no worrisome trends.

Overall Risk-Benefit Assessment:

Efficacy has been adequately demonstrated for DRSP/EE in the treatment of PMDD. A statistically significant advantage to DRSP/EE over placebo on the primary efficacy endpoint, change from baseline in the first 21 items of the DRSPS, was demonstrated. The clinical relevance of this finding was supported by statistically significant findings of efficacy on a number of secondary endpoint measures, particularly those assessing function and global improvement at the time of the luteal phase. In addition, comparisons to similar data obtained in trials of SSRIs for PMDD suggest that the treatment effect of DRSP/EE on PMDD symptomatology is similar to that of these approved products.

The safety profile for DRSP/EE as evidenced in this trial is acceptable. No deaths or VTEs occurred over the three cycles of treatments. Few SAEs occurred, and these were not believed to be attributable to DRSP/EE. The adverse events that occurred more commonly among DRSP/EE subjects are those that tend to be associated with oral contraceptive use in general. There was no indication of any cardiovascular adverse events that might be attributable to hyperkalemia. Laboratory values were reassuring in demonstrating no adverse impact on potassium levels, although, as known for oral

contraceptives generally, there was an adverse impact of DRSP/EE on triglycerides and total cholesterol. There were no notable effects on vital signs.

While the treatment effect of DRSP/EE on symptoms of PMDD may be seen as moderate, it has been demonstrated to be similar to that observed with use of the SSRIs currently approved for the PMDD indication. Availability of an oral contraceptive product for treatment of PMDD would offer several advantages over use of an SSRI: in women already using oral contraception, a single drug could address both health needs, and potential adverse effects of SSRIs, ranging from sexual dysfunction to possible increased suicidality, could be avoided.

10.2 Review of Individual Study Report for Protocol 305141 (Report A07545)

10.2.1 Summary

Title: "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg/Ethinyl Estradiol 20 μg (as Beta-Cyclodextrin Clathrate), in the Treatment of Premenstrual Dysphoric Disorder (PMDD)" dated 19 November 2004.

Three amendments were made to Study 305141. The first, dated May 3, 2002, included the following changes:

- Modification of entry criteria to allow smokers up to age 34 and women with BMI up to 37 to participate

Amendment 2, dated July 1, 2002, included the following changes:

- Revised allowable BMI back to < 35

Amendment 3, dated July 10, 2003, included:

- Changed requirement regarding meeting DSM-IV criteria for PMDD diagnosis to state that subject must have met the criteria during the two run-in menstrual cycles, rather than having met them in each of the two cycles
- Extension of timeline due to difficulty recruiting subjects
- Discontinuation of trial after enrollment of 65 of 126 planned subjects, due to difficult recruitment
- Redefinition of Per Protocol analysis population to include requirement for completion of at least one treatment cycle in each treatment period

Medical Reviewer's Comment:

- ***It is unlikely that the amendment concerning satisfaction of DSM-IV criteria for PMDD diagnosis would have changed the qualifying procedure, as the DSM-IV criteria state that "Criteria A, B and C must have been confirmed by prospective daily ratings during at least two consecutive symptomatic cycles."***

First patient entered: January 2002

Last patient completed: October 2003

10.2.2 Objectives

The primary objectives of this study were to assess the efficacy and safety of DRSP/EE compared to placebo in treating the symptoms of PMDD. Efficacy was evaluated by looking at change from baseline in the sum of the averages over the five days preceding menses in the first 21 items on the DRSPS, averaged over the three treatment cycles.

Medical Reviewer's Comment:

- ***In discussions with the Applicant during development of these protocols, DNDP recommended that luteal phase DRSPS ratings be obtained over the full seven days of the late luteal phase. Although subjects completed this instrument daily, the Applicant has only provided data over the five days preceding menses. However, as noted in the Reviewer's Comment in Section 10.1.2, the reviewer does not believe that use of the shorter luteal phase period compromises the validity of the data.***

10.2.3 Overall Design

This phase 3, U.S. multicenter, randomized, double-blind, placebo-controlled crossover study was designed to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in the treating symptoms of PMDD over a total of seven menstrual cycles. Following a two cycle run-in phase, subjects diagnosed with PMDD by DSM-IV criteria were enrolled in a treatment phase consisting of three menstrual cycles of randomized treatment with DRSP/EE or placebo (Treatment Period 1 [TP1]), a one-cycle wash-out period, then three cycles of treatment with the alternate test article (Treatment Period 2 [TP2]). Subjects were randomized to DRSP/EE or placebo in a 1:1 ratio.

The study was conducted at 17 sites in the U.S, although 24 sites participated in screening subjects. The recruitment goal was 126 subjects; actual enrollment was 64 subjects, following early termination of the protocol due to recruitment difficulties. The planned sample size was to provide 90% power to detect a difference of 6.5 points (SD 18) in the DRSPS score change from baseline between treatment and placebo arms, assuming a 30% drop-out rate and a correlation of 0.50 between the within-subject measurements from the two treatment periods.

Medical Reviewer's Comments:

- ***No power calculation was provided for the amended sample size obtained in this study.***

10.2.4 Study Procedures and Conduct

10.2.4.1 Schedule of Study Assessments

Subjects were screened for eligibility at Visit 1 and procedures indicated in Table 48 were performed. Subjects were historically screened based on DSM-IV criteria for PMDD (see Table 25), and those with past and present psychiatric disorders other than PMDD were excluded based upon the Structured Clinical Interview for DSM-IV (SCID), which was usually administered at Visit 3, but could be administered as early as Visit 1 or 2. Subjects who were in days 1-6 of their menstrual cycles at Visit 1 also had Visit 2 procedures performed at the initial visit. Subjects were then instructed to record daily ratings of PMDD symptoms using the DRSPS instrument, beginning on the first day of the next menses following Visit 1. Two run-in visits occurred at days 5-10 of menstrual cycles 1 (Visit 2) and 2 (Visit 3) following screening. At both visits, the completed DRSPS ratings were reviewed, and at Visit 2, eligibility was reconfirmed, and the PMTS, SF-36 and Q-LES-Q instruments were administered. Physical and gynecological exams and laboratory assessments were performed at Visit 3. At Visit 4, subjects were randomized, and provided with 3 cycles of study drug. At this visit, and at each monthly visit thereafter, efficacy and safety measures were obtained as indicated in the Schedule of Assessments. Eight clinical visits occurred during the treatment phase. During TP1, Visits 4-6 occurred on days 1-3 of treatment cycle 1 (menstrual cycle 3) and days 1-4 of treatment cycles 2 and 3, respectively. Visit 7 occurred on days 1-4 of menstrual cycle 6, the beginning of the washout period. During TP2, Visits 8-10 occurred on days 1-3 of treatment cycle 4 and days 1-4 of treatment cycles 5 and 6. An EOT visit, Visit 11, was conducted on days 5-10 of the 10^{th} menstrual cycle. Subjects who withdrew prior to EOT underwent Visit 11 procedures upon withdrawal.

Table 48 Study 305141: Schedule of Study Assessments

	Screen Visit (Visit 1)	Run-in Cycle 1 (Visit 2)	Run-in Cycle 2 (Visit 3)	Treatment Cycle 1 (Visit 4)	Treatment Cycle 2 (Visit 5)	Treatment Cycle 3 (Visit 6)	Washout Cycle (Visit 7)	Treatment Cycle 4 (Visit 8)	Treatment Cycle 5 (Visit 9)	Treatment Cycle 6 (Visit 10)	Post Treatment (Visit 11)
Cycle day	Anyb	5-10b	5-10	1-3	1-4	1-4	1-4	1-3	1-4	1-4	5-10
Informed consent	X										
Randomization				X							
In/exclusion criteria	X	X	X	X							
Instruct (I) /review (R)/collect (C) DRSPS	I	R	R, C	R, C	R, C	R, C	R, C	R, C	R, C	R, C	R, C
History and baseline Info	X										
Weight, blood pressure, heart rate, temperature		X d	X	X	X	X	X	X	X	X	X
Contraceptive method	X	X	X	X	X	X	X	X	X	X	X
DSM-IV criteria	X-			X-							
SCID e	X	X	X								
Pregnancy test (urine [U]/serum [S]) b	X-U	X-U	X-S	X-U	X-S	X-U	X-S	X-U	X-S	X-U	X-S
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Endocervical sample			X								
Physical & gyn. exam			X				X				X
Pap smear			X								X
Hematology/Chemistry c			X		X		X		X		X
Urinalysis			X				X				X
CGI				X d	X	X	X	X	X	X	X
Scales for PMTS		X		X			X	X			X
SF-36		X		X			X	X			X
Endicott Q-LES-Q		X		X			X	X			X
Drug dispensed/returned				X-3 cycles dispensed	X-returned	X-returned	X-returned	X-3 cycles dispensed	X-returned	X-returned	X-returned

Source: Text Table 2, a07545.pdf, pp 26-7

10.2.5 Study Drug

10.2.5.1 Dose Selection

The drug studied was DRSP 3 mg/EE 20 μg, administered for 24 days, followed by 4 days of inert tablets. Subjects in the placebo arm received a daily placebo tablet for all 28 days of each cycle.

Medical Reviewer's Comment:

- ***The dose selection was not directly based on the drug's effect on PMDD symptoms. While suppression of ovulation is a useful pharmacodynamic measure for DRSP/EE's contraceptive indication, it is a surrogate marker of unproven validity for the drug's utility for the PMDD indication.***

10.2.5.2 Choice of Comparator

DRSP/EE was compared against placebo due to the known high rate of nonspecific response to treatment seen in PMDD.

10.2.5.3 Assignment to Study Drug

Subjects were randomized to treatment sequence in a 1:1 ratio at Visit 4, based on permuted block randomization.

10.2.6 Patient Population

Subjects in this study were women with PMDD diagnosed by the DSM-IV criteria, as observed over two menstrual cycles.

10.2.7 Inclusion and Exclusion Criteria

The DRSPS instrument, used extensively in determining eligibility, is displayed in Table 26.

Inclusion Criteria

- PMDD by DSM-IV criteria
  - At screening, by history
  - At the end of the second run-in cycle, by review of symptom records
- Any 5 distinct items, without overlap, on the DRSPS (see Table 26) (each of the 2 consecutive baseline run-in cycles must have fulfilled the following criterion):
  - Luteal phase daily average ≥3.0.
- DSRP scale (each of the 2 consecutive baseline run-in cycles must have fulfilled the following criteria):
  - Follicular phase daily average score of ≤2.5 for each item on the DRSPS for nonphysical symptoms only. However, only one of the physical symptoms that were >2.5 in the follicular phase could have been a symptom in the 5 items needed for the inclusion criterion above. The average was to be computed for days 6-10 of the cycle, and entries in the dairy must have been present for at least 3 of these days for the item to be used as an inclusion criterion for that month.
  - Late luteal phase daily average score at least twice as high as the corresponding follicular phase daily average score for 3 of the 5 distinct items without overlap. At least one item must have represented a nonphysical symptom.
  - Functional impairment items required a score of ≥3 on at least 1 of the 3 impairment items for ≥2 luteal days

- Absence of an existing and/or a history of the following Axis I disorders during the last 2 years based on the SCID:
  - Major depressive disorder
  - Anxiety disorder (panic, obsessive-compulsive, posttraumatic stress)
  - Eating disorder
  - Drug and/or alcohol disorder
- Absence of an existing and/or a history (lifelong) of the following Axis I disorders based on the SCID:
  - Bipolar disorder
  - Psychotic disorder
  - Somatoform disorder
  - Dysthymic disorder
- Healthy volunteer
- 18-40 years, smokers maximum of 34 at inclusion
- Non-suspicious Pap smear within 6 months before study medication. For an ASCUS Pap, either a negative HPV or benign subtype required on HPV testing. Any results worse than LGSIL excluded.
- No oral contraceptives for at least 3 months prior to enrollment
- At least 3 menstrual cycles subsequent to delivery, abortion or lactation before the Visit 1
- Regular menstrual cycles (length between 25-34 days) in the 3 month period preceding Visit 1
- Negative pregnancy test before first dose
- All subjects needing contraception to use a barrier method during the study
- Signed informed consent
- Would comply with protocol

Exclusion Criteria

- Any formal psychotherapeutic counseling within 1 month of screening, or used medication for PMS or PMDD, including hormones, bromocriptine, GnRH agonists, Vitamin B6 (> 100 mg), calcium supplements (>1500 mg/day), anxiolytics and antidepressants during the 3 months prior to screening Visit 1
- Used sleeping medication, including melatonin, more than 3 days per month
- Pregnant or lactating
- Known hypersensitivity to any of the study drug ingredients
- Any disease or condition that could compromise the function of body systems that could result in altered absorption, excessive accumulation, impaired metabolism or altered excretion of the study drug
- Severe systemic disease that might interfere with conduct of the study or interpretation of results
- Uncontrolled thyroid disorder
- Current or history of clinically significant depression in the past 2 years
- Abnormal, clinically significant findings which could worsen under hormonal treatment
- Use of an experimental drug or participation in another clinical trials within 3 months prior to enrollment
- Liver disease: previous, acute and chronic progressive liver diseases. An interval of at least 6 months required between resolution of viral hepatitis and beginning of study drug intake
- Vascular disease: existing or previous venous or arterial thromboembolic diseases or any condition that could increase the risk of any of the above mentioned disorders (including

coagulopathies, hereditary deficiencies, family history, specific heart diseases, cardiac or renal dysfunction and clinically significant varicose veins or previous phlebitis)

- Uncontrolled hypertension (>140/90) or medication for hypertension
- Kown diabetes, blood glucose > 140 mg/dl
- Sickle cell anemia
- Clinically significant abnormal lipid metabolism
- History of estrogen-related malignancies, including breast, endometrial and ovarian. Women with other malignancies/premalignancies eligible for inclusion if recurrence-free for at least 5 years
- History, current or suspicion of: pemphigoid gestations, otosclerosis, endometrial hyperplasia, complicated migraine, genital bleeding of unknown origin, clinically significant fibroids or kidney disease with impaired renal function
- Use of illicit drugs, alcohol or medicine abuse (e.g., laxatives)
- Use of additional sex steroids, hydantoins, barbiturates, phenobarbital, phenytoin, primidone, carbemazepine, rifampin, Ritalin, herbal products or dietary supplements for treatment of PMS/PMDD, or continuous use of antibiotics for more than 10 days
- Use of oral contraceptives, injectable estrogens, progestogens or androgens during 3-month period prior to screening; used hormonal contraceptive implant within 1 year, other hormonal contraceptive methods such as hormonal IUD
- Have used or are using Accutane within 30 days; medication, herbals or over the counter formulas to control weight gain or aid weight loss, use of calcium supplements and/or Vitamin B6 if not used during the qualification phase or a change in dosage
- BMI ≥35
- History of porphyria
- History of herpes of pregnancy
- Positive Gonorrhea or Chlamydia test (if treated, with negative repeat culture, could be included)
- Clinically relevant pathological safety laboratory results
- Previous participation in a study involving the same or similar medication for treatment of PMS

Medical Reviewer's Comment:

- ***Inclusion and exclusion criteria are generally the same as those used for Study 304049.***

10.2.7.1 Demographics and Baseline Disease Characteristics

Seventeen US sites each enrolled 1 to 15 subjects. All of the 64 subjects randomized received at least one dose of study medication and constitute the ITT population. The sequence DRSP/EE→placebo had 34 subjects; placebo→DRSP/EE had 30 subjects randomized. Of the 64 subjects, 25 completed both treatment periods - 14 in the DRSP/EE→placebo sequence and 11 in the placebo→DRSP/EE sequence. Over the two treatment periods, 54 subjects were exposed to DRSP/EE and 49 to placebo. The "Per Protocol" (PP) population, defined as subjects took no prohibited medications, had ≥ 75% compliance, completed at least one treatment cycle in each sequence and had no violations of inclusion/exclusion criteria, consisted of 12 subjects in the DRSP/EE→placebo sequence and 11 in the placebo→DRSP/EE sequence.

Demographic characteristics are summarized in Table 49. There was a statistically significant difference between the groups on average cycle length, with the DRSP/EE→placebo mean length exceeding that in the placebo→DRSP/EE by 1.2 days. Duration and intensity of menstrual bleeding and occurrence of intermenstrual bleeding were similar between groups.