

Postmarketing Study

As part of the risk management program for YAZ, the International Active Surveillance (INAS) Study began in the USA in August 2005. The study began with recruitment of Yasmin (DRSP 3mg/EE 0.03 mg) and other OC initiators. Recruitment of YAZ initiators first began following its market introduction in late April 2006. At the end of July 2006, more than 10,000 women have been enrolled into the study, including approximately 1,000 YAZ initiators. Extension of the study into Europe will depend on the international registration and launch status of YAZ.

Periodic Adverse Event Reporting

The first Periodic Adverse Drug Experience Report for YAZ NDA 21-676, approved on March 16, 2006, for the indication of oral contraception, was submitted on July 14, 2006 (reporting period March 16, 2006 – June 15, 2006). Three initial non-serious reports were included, blue stools, pain and burning in left forearm and thigh, and severe acne.

Medical Officer Comment:

- *In summary, there is no safety information from this update that would impact on approvability or labeling.*

8 ADDITIONAL CLINICAL ISSUES

8.4 PEDIATRICS

As noted in the original review, 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 Comment:

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

8.7 POSTMARKETING RISK MANAGEMENT PLAN

The planned post-marketing risk management activity for YAZ in regard to potential hyperkalemia is discussed in the review of NDA 21-676 and is comparable to the risk management plan that was conducted for Yasmin.

For NDA 21-873, the risk management plan specifically targets the clinical issues of PMDD. The Applicant submitted a brief outline of its "Educational Outreach Protocol for Providers and Patients" in the Complete Response. The stated objectives of the program according to the Applicant are to:

- Educate healthcare providers on the diagnostic criteria and the various existing tools to differentiate and identify the various premenstrual disorders
- Educate healthcare providers on the interpretation of one of the tools (the Daily Record of Severity of Problems) [DRSPS, the instrument used for the primary endpoint in the PMDD trials] used to assess the severity of a patient's premenstrual disorder
- Educate healthcare providers on the treatment options
- Educate women on the advantages of using diaries to better understand their symptomatology, and foster better discussion with their healthcare provider
- Provide women with opportunities to increase their understanding and awareness of PMDD and the treatment options available to them

Medical Reviewer's Comments:

- ***The Division contacted the Applicant twice through teleconference (August 24th and 31st, 2006) to discuss the educational and training program submitted at the time of the Complete Response on March 1, 2006. The Division initially wanted more specifics on the program. When the Division learned that the health provider education assessment for PMDD and PMS was incorporated into a very large postmarketing survey that included a great deal of general marketing questions, the Applicant was asked to narrow their survey approach to cover just PMDD and PMS issues.***

- ***In the Applicant's September 14, 2006 submission they provide written responses to the Division's comments during these teleconferences. These responses include the following:***
 - Berlex will provide clear statements that YAZ is first and foremost an oral contraceptive. It should be used for PMDD only in women choosing to use an oral contraceptive for the purpose of birth control.

 - Berlex educational outreach for patients and health care providers (HCPs) will establish a clear understanding of what PMDD is. For HCPs, we will educate them on the DSM-IV criteria, including the use of a prospective diary. For patients, they will be encouraged to complete a prospective daily diary to use in their discussions with their HCPs.

 - Materials provided to HCPs will include information about how to diagnose PMDD, such as the DSM-IV criteria for diagnosis of PMDD.

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- *After reviewing the Applicant's September 14, 2006 submission this reviewer has the following comments:*

 - *The educational assessment of health care providers is now much shorter and focused primarily on PMDD and PMS.*
 - *An acceptable health care provider guide to the DSM-IV criteria for PMDD is provided.*
 - 
 -

8.8 OTHER RELEVANT MATERIALS

The Division of Drug Marketing, Advertising and Communications (DDMAC) made recommendations on the Package Insert and the Patient Package Insert. DDMAC found the proprietary name YAZ acceptable.

The Division of Surveillance, Research and Communication Support (DSRCS) made recommendations regarding patient labeling.

The Division of Medication Errors and Technical Support (DMETS) recommended against the use of the proprietary name YAZ and made additional recommendations regarding labeling. DRUP considered the DMETS concerns that the name YAZ might be misinterpreted as an abbreviation for Yasmin. The Division believes that such an error is unlikely, and even if it were to occur, the patient would receive an approved oral contraceptive and thus, would not risk an unplanned pregnancy or other untoward outcome due to receipt of an unintended drug.

Labeling recommendations from DDMAC, DSRCs and DMETS were considered by DRUP and those judged to have a significant impact on appropriate use of the product were conveyed to the Applicant. Labeling acceptable to both the Division and the Applicant was successfully negotiated.

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS

YAZ is safe and effective for the secondary indication of PMDD for women who desire this product for contraception.

9.2 RECOMMENDATION ON REGULATORY ACTION

I recommend that NDA 21-873, drospirenone (DRSP) (3 mg) /ethinyl estradiol (EE) (0.02 mg) oral tablets (YAZ), be approved for the secondary indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception."

This recommendation is based on the following:

- The submissions referenced in the approvable letter (December 2, 6, 9, 2005 and January 10, 2006) which were not reviewed prior to the January 23, 2006 approvable letter for NDA 21-873 have now been reviewed. There are no safety concerns in those submissions that would impact approval of YAZ for the secondary indication of PMDD. These submissions included safety data from the Applicant's finalized acne studies (306820 & 306996) and unfinalized European contraceptive studies (308020 & 308021).
- Final study reports from European contraceptive trial protocols 308020 & 308021 submitted on August 8, 2006 show no safety concerns. No new safety concerns were identified on the last safety update which was also submitted on August 8, 2006. This safety update is current up through August 7, 2006.
- YAZ was approved for the primary indication of contraception on March 16, 2006 thus allowing for approval of secondary indications.
- Acceptable labeling has been received from the Applicant.
- I concur with the primary reviewer (Lisa Soule, MD) and secondary reviewer (Scott Monroe, MD) that the clinical studies (304049 & 305141) under NDA 21-873 which focused specifically on the secondary indication of PMDD showed that YAZ was both safe and effective.

9.3 RECOMMENDATION ON POSTMARKETING ACTIONS

Postmarketing actions that are already in place for YAZ (via the contraceptive NDA 21-676) include a Phase IV Commitment surveillance study for arterial and venous thromboembolic events and a risk management plan similar to Yasmin in regard for the potential for hyperkalemia. Specific risk

management in regard to prescribing for PMDD are discussed in section 8.7 and summarized in the subsequent section.

9.3.1 Risk Management Activity

The principal risk management activity for this secondary indication of PMDD is addressed through labeling. Labeling for this product stresses that women should initially decide to use this product primarily for birth control and that PMDD is a secondary indication and benefit. The label cautions women not to use YAZ primarily for treatment of PMDD unless they have already decided to use an oral contraceptive for birth control since there are other medical alternatives. The label also addresses the fact that PMDD is a serious mood disorder and should be diagnosed by clinicians according to strict criteria.

The modifications made by the Applicant in their educational and training program (submitted September 14, 2006) are acceptable. These modifications include a health care provider assessment that is shorter and more appropriately focused on PMDD & PMS; an educational guide to the DSM-IV criteria of PMDD; and an Ingenix study to assess prescribing practices.

9.3.2 Required Phase 4 Commitments

As discussed in the March 16, 2006 review of NDA 21-676; the Applicant has committed to conducting a large prospective Phase 4 postmarketing safety study with YAZ. This study is called the International Active Surveillance (INAS). The INAS study is similar to the recently completed 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 INAS 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. Recruitment of YAZ initiators first began in the U.S. following its market introduction in late April 2006. At the end of July 2006, more than 10,000 women have been enrolled into the study, including approximately 1,000 YAZ initiators. Extension of the study into Europe will depend on the international registration and launch status of YAZ.

No additional Phase 4 commitments are required.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 LABELING REVIEW

Labeling negotiations were concluded successfully. As compared to the approved YAZ label for contraception, the main goal for this label was to stress that women should not use YAZ for the treatment of PMDD unless they have already decided to use an oral contraceptive for birth control as noted in other sections of this review.

9.5 COMMENTS TO APPLICANT

There are no comments to convey to the Applicant.

REFERENCES

¹ Cochrane Database of Systematic Reviews, Issue 4, 2002, updated August 28, 2002

² Premenstrual Syndrome, ACOG Practice Bulletin #15, April, 2000

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/s/

Gerald Willett
9/28/2006 10:29:14 AM
MEDICAL OFFICER

Lisa Soule
9/28/2006 12:54:51 PM
MEDICAL OFFICER
I concur with Dr. Willett's conclusions and recommendation.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-873
Submission Code	N-000
Letter Date	December 22, 2004
Stamp Date	December 23, 2004
PDUFA Goal Date	October 21, 2005 (clock extended to January 23, 2006)
Reviewer Name	Lisa M. Soule, M.D.
Review Completion Date	January 20, 2006
Established Name	Drospirenone/Ethinyl Estradiol
(Proposed) Trade Name	YAZ
Therapeutic Class	Combined Oral Contraceptive
Applicant	Berlex
Priority Designation	S
Formulation	Tablet
Dosing Regimen	Drospirenone 3 mg/Ethinyl Estradiol 0.02 mg daily for 24 days followed by placebo for 4 days
Indication	Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have no known contraindications to oral contraceptives and who desire contraception

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that NDA 21-873, DRSP (3 mg) /EE (0.02 mg) oral tablets (YAZ), be approved for the indication of "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose 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.

1.2 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).

1.2.1 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.

1.2.2 Required Phase 4 Commitments

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.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two phase 3, randomized, double-blind, placebo-controlled, multicenter trials were conducted in the U.S. to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in treating symptoms of PMDD. The population studied in each trial comprised women diagnosed with PMDD by DSM-IV criteria.

Study 304049 was a parallel group trial, in which 450 subjects participated in 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, with 232 subjects randomized to DRSP/EE and 218 to placebo. The study was conducted at 64 sites in the U.S.

Study 305141 was a crossover study conducted over a total of seven menstrual cycles. Following a two cycle run-in phase, subjects 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 planned to enroll 126 subjects; however, following early termination of the protocol due to recruitment difficulties, actual enrollment was only 64 subjects. Of these, 34 were randomized to the sequence DRSP/EE→placebo, while 30 were randomized to the placebo→DRSP/EE sequence. The study was conducted at 17 sites in the U.S.

1.3.2 Efficacy

The Daily Rating of Severity of Problems Scale (DRSPS) was used to assess the effect of treatment. Subjects completed this questionnaire daily, beginning on the first day of menses in run-in Cycle 1. 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, each of the first 21 items was averaged over the five days preceding menses, and the averages were 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 cycle scores averaged per subject) from the baseline score, which was averaged over the two run-in cycles.

In both studies, the primary efficacy analysis of the Full Analysis Set, an 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 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 from 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 general convention¹, 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 historical 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 that of the fluoxetine luteal phase dosing trial, which used the identical outcome measure over the same treatment period, the changes from baseline in DRSPS score with treatment by the active study drug were -28 to -31 depending on fluoxetine dose, compared to -37.5 for DRSP/EE in Study 304049 and -17 to -34 for DRSP/EE in Study 305141, depending on treatment sequence. The magnitude of the difference between active 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 by the Division of Neuropharmacologic Drug Products.

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).

1.3.3 Safety

There were no deaths in either of the trials. There were a total of five serious adverse events (SAEs), three occurred in subjects exposed to DRSP/EE (1.1%) and two occurred in subjects during placebo exposure (0.7%). The only SAE occurring in a DRSP/EE subject that was considered possibly drug-related by the Applicant (severe dysplasia on Pap smear) was not judged by the reviewer to be drug-related.

Adverse events occurred in 79% of DRSP/EE subjects and 64% of placebo subjects. A greater proportion of subjects taking DRSP/EE withdrew prematurely (30.5% vs. 24% of placebo subjects), with most of the discrepancy attributable to the number who withdrew due to adverse events (14.0%, compared to 4.1% of placebo subjects). Events that were judged to be treatment-related and differentially distributed across treatment groups included: intermenstrual bleeding, nausea, breast pain, decreased libido, emotional lability, menorrhagia and migraine, all of which occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo. These events are known to be associated with oral contraceptive use, and are listed in class labeling for combination hormonal contraceptive products.

Special attention was paid to adverse events of particular concern, including cardiovascular events possibly related to hyperkalemia and venous thromboembolic events (VTEs). A total of 12 subjects over the two trials experienced cardiovascular events identified as possibly resulting from hyperkalemia (2.8% of DRSP/EE subjects and 1.5% of placebo subjects); however, none of these subjects had a potassium (K^+) level above the normal range at any measurement. There were no VTEs in either trial. A total of five pregnancies occurred, three clearly conceived during or shortly after placebo treatment. In the remaining two cases, in which subjects recently on DRSP/EE conceived, the estimated date of conception for one was three weeks after the last dose and the second pregnancy was diagnosed 33 days after the last dose of DRSP/EE.

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 above the normal range on treatment.

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

1.3.4 Dosing Regimen and Administration

The dosing regimen proposed is DRSP 3 mg/EE 20 μ g, 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.

1.3.5 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 $AUC_{(0-T_{last})}$ 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.

1.3.6 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; in fact, women with diabetes, liver 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 on patients with such concomitant conditions cannot be assessed from the population studied. The proposed labeling would contraindicate DRSP/EE in women with hepatic dysfunction and moderate to severe renal dysfunction, as does the current Yasmin label.

**APPEARS THIS WAY
ON ORIGINAL**

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Drospirenone (DRSP) is a 17-alpha-spironolactone derivative with antimineralocorticoid and antiandrogenic properties. The active estrogen moiety in this product is ethinyl estradiol (EE), which is complexed with β -cyclodextrin clathrate to protect against degradation.

2.2 Currently Available Treatment for Indications

Three drugs, all selective serotonin-reuptake inhibitors (SSRIs), (fluoxetine [Sarafem®], paroxetine [Paxil®] and sertraline [Zoloft®]) are marketed in the US for this indication. Recommended dosing includes either daily dosing throughout the menstrual cycle or dosing limited to the luteal phase of the cycle. The Cochrane Database of Systematic Reviews² concluded that there is "very good evidence to support" the use of SSRIs in treatment of PMDD.

Oral contraceptives are also used off-label for treatment of PMDD. However, the American College of Obstetrics and Gynecology (ACOG) recommended in 2000³ that management strategies proceed in a stepwise manner, beginning with supportive therapy, including diet, exercise and nutritional supplements, then moving on to SSRIs as needed, with hormonal ovulation suppression, using oral contraceptives or gonadotropin releasing hormone (GnRH) agonists as third line agents.

2.3 Availability of Proposed Active Ingredient in the United States

Yasmin (also known as Yasmin 30), a combined oral contraceptive approved for marketing in the U.S. on May 11, 2001, contains the same two ingredients, although the EE dose is higher, 30 μ g, and the product is administered as 21 days of active tablets followed by 7 days of placebo tablets. The currently proposed regimen represents an increase of 9 mg in the total monthly dose of DRSP, and a decrease of 150 μ g in the total monthly dose of EE.

2.4 Important Issues with Pharmacologically Related Products

Yasmin is marketed in over 40 countries worldwide. An extensive ongoing postmarketing pharmacoepidemiologic surveillance program for Yasmin is discussed in the review of NDA 21-676.

The Applicant submitted NDA 21-676 requesting marketing approval for the same product for the indication of prevention of pregnancy. NDA 21-676, submitted October 17, 2003, studied two dosing regimens, a 21-day and a 24-day regimen, but requested approval only for the 24-day regimen. The 24-day regimen received an approvable action on November 17, 2004. The Division of Reproductive and Urologic Products (DRUP) indicated that approval could be obtained either by demonstrating a clinical benefit for the 24-day regimen over that provided by the 21-day regimen to offset the potential increased risk from the additional three days of treatment, or by proposing to market the 21-day regimen. Demonstration of clinical benefit could be achieved by demonstrating fewer "escape ovulations" with the 24-day vs. the 21-day regimen, or by demonstrating safety and efficacy for either of two proposed secondary indications, PMDD or acne.

2.5 Presubmission Regulatory Activity

IND 61,304 was opened on November 21, 2000, to study the use of YAZ for the treatment of PMDD. The primary indication for this drug was to be prevention of pregnancy, with PMDD treatment proposed as a secondary indication. The PMDD indication initially was assigned to DNDP until the fall of 2003, when it was transferred to DRUP along with all other drug products for PMDD.

The Applicant had a guidance meeting with DNDP on January 23, 2001 to discuss Protocol 304049, the pivotal study for the PMDD indication. At this time, it was agreed that:

- Enrollment of a population of women with PMDD but not seeking oral contraception was scientifically acceptable, but might pose ethical problems, as these women would be exposed to a second component (EE) that is not essential to treatment of PMDD
- The use of the Daily Record of Severity of Problems Scale (DRSPS) was acceptable to DNDP; additionally that the Applicant could focus on the affective symptoms measured by the scale and drop the physical symptoms
- The study design was acceptable, although issues were discussed regarding validating that diary entries were made on a daily basis
- A negative study using Yasmin 30 in a 21-day regimen could not be used as either a pivotal or a supportive study for the PMDD indication
- Luteal phase DRSPS ratings were recommended to be obtained over the full 7 days of the phase, rather than 5 of 7 days as proposed. If the Applicant does not adopt this recommendation, a rationale should be submitted to support this decision
- Evaluation of weight change, measured once per cycle, at the same time in each cycle, was acceptable, but as this is a secondary outcome, data could not be presented in labeling
- A proposed cross-over design was acceptable, provided that a sufficient wash-out period between treatments were provided; the protocol should be submitted for statistical review
- The method of weighting the ANCOVA should be further specified
- An alternative analysis plan should be provided in case the assumption of normality does not hold; information about tests and standards for normality should be submitted
- Procedures for handling of missing data should be clarified; the Division recommended that missing item scores be handled by averaging non-missing scores and imputing the averaged value
- A detailed statistical analysis plan would be submitted several months before unblinding

Comments from the statistics reviewer, following review of a revised protocol, were conveyed to the Applicant in October 2001, and included:

- Concern that the proposed rule for handling missing data could result in exclusion of a subject who received medication, and had at least one post-randomization measurement from the ITT population. The Applicant was asked to clarify and refine this rule, to propose sensitivity analyses to verify the robustness of the data obtained, and to provide an overall summary of missing data observed.
- Requests for clarification of weighting factors to be used in the weighted analysis and for detailed criteria for defining violations of normality

- Further statistical comments on a revised protocol were provided in March 2002; these reiterated the earlier comment on handling of missing data and asked the Applicant to prespecify the model to be used for analyzing secondary variables by ANCOVA.
- The Statistical Analysis Plan for Protocol 305141 was submitted in October 2003, and found to be acceptable to DRUP statisticians. However, it was noted that the trial was stopped prior to meeting enrollment goals, and thus, that the trial might not support the proposed objectives.
- The Statistical Analysis Plan for Protocol 304049 was submitted in May 2004 and was similarly acceptable to DRUP statisticians. Previous comments about handling of missing data were again emphasized, noting the possibility that a subject could take the study drug, have at least one post-randomization measurement, and still be excluded from the ITT population. Sensitivity analyses for different methods of handling missing data and a summary of patterns of missing data were requested. The Applicant responded by clarifying that subjects with as few as 2 days (of 5 collected) worth of outcome data in the post-baseline period would be included in the ITT population. The methods of imputation of missing data could allow a subject to be excluded from the ITT population if she were missing 3 days of data in the 5 day period assessed, and would definitely result in exclusion of subjects missing 4 or more days of data. The Applicant further dismissed the need for sensitivity analysis to verify the robustness of the data analysis.

A pre-NDA meeting was held by DRUP regarding the PMDD indication in October 2004. Comments made at that time included:

- Concern about the adequacy of Study 305141 and the possibility of bias due to early termination of the trial. The Applicant noted that the study was discontinued due to slow enrollment, and that it remained blinded at discontinuation.
- The length of the wash-out period in this cross-over trial, with potential residual treatment effect, will be a review issue
- Concern about blinding being compromised by the impact of YAZ on subjects' menstrual cycles and timing of withdrawal bleeding. Demonstration of efficacy in the first month of treatment would help allay these concerns.
- Clinical benefit as well as statistical significance of efficacy measures will need to be demonstrated. This will entail providing a value for the minimally important clinical difference (MICD) between YAZ and placebo subjects, as well as describing the methods by which this value was determined to be of clinical significance.

2.6 Other Relevant Background Information

- NDA 21-676, for the contraceptive indication for YAZ, was submitted in 2003. An approvable action was issued for this NDA on November 17, 2004, with the requirement that the Applicant either demonstrate a clinical benefit for the 24-day regimen, as compared to a 21-day regimen, that would justify the potential risk due to the additional 3 days of drug administration, or that a 21-day regimen be proposed for marketing. The Applicant was further informed that demonstration of a clinical benefit could be accomplished by demonstration of fewer "escape ovulations," or by showing safety and efficacy for either of the two proposed secondary indications, PMDD and acne.
- The current NDA combines the two indications of treatment of PMDD and pregnancy prevention, with cross-reference to NDA 21-676 for the information supporting the contraceptive indication.

National approval of the 21-day regimen of DRSP 3 mg /EE 2 µg (marketed under the name Yasminelle) was granted in the Netherlands, the Reference Member State, on August 4, 2005. The product has not yet been marketed. (This information is derived from the Applicant's submission of December 13, 2005.)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

YAZ combines two drug substances, DRSP and EE complexed with β-cyclodextrin clathrate, in tablet form. The β-cyclodextrin clathrate is considered an excipient, used to stabilize the 20 µg dose of EE. DRSP is the same drug substance as that used in the approved product, Yasmin; the DMF referenced for DRSP was considered adequate by the Chemistry Reviewer. The referenced DMFs for EE and β-cyclodextrin clathrate were also found to be adequate. Based on stability data submitted in the NDA, granting of an expiry of 48 months is recommended. The Chemistry Reviewer recommended approval of the NDA, pending acceptable labeling. Labeling comments by the Chemistry Reviewer are discussed in Section 9.4.

No clinical microbiology was indicated or studied.

3.2 Animal Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer recommends approval of NDA 21-873, based on the similarity in composition and intended treatment populations to the Applicant's previously approved product, Yasmin. There are no nonclinical safety issues relevant to clinical use.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data sources for this NDA are the two phase 3 trials evaluating the safety and efficacy of DRSP/EE for treatment of symptoms of PMDD, Study 304049 and Study 305141.

4.2 Tables of Clinical Studies

Table 1 provides an overview of each clinical trial in the clinical development plan for the PMDD indication, including information regarding study design, number of patients enrolled and trial duration.

Table 1 Summary of Studies Providing Efficacy and Safety Data

Report/Protocol Number	Study Type Phase	Study Design	Study Medication	Duration of Treatment (regimen)	Number of Subjects Treated	Age Range in Years (Mean)
A21566/304049	Efficacy/Safety Phase 3	Multicenter, randomized, double blind, placebo-controlled, parallel	DRSP/EE	3 cycles (24-day regimen)	231	18-40 (31.0)
			Placebo		218	18-42 (32.0)
A07545/305141	Efficacy/Safety Phase 3	Multicenter, randomized, double blind, placebo-controlled, crossover	DRSP/EE; Placebo ^a	6 cycles (24-day regimen)	34	19-39 (31.0)
			Placebo; DRSP/EE ^b		30	20-40 (33.0)

DRSP = drospirenone; EE = ethinyl estradiol; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg.

^a Treatment group first received DRSP/EE for 3 treatment cycles, then no study medication for 1 cycle, and then placebo for 3 treatment cycles.

^b Treatment group first received placebo for 3 treatment cycles, then no study medication for 1 cycle, and then DRSP/EE for 3 treatment cycles.

Source: Text Table 1, ise.pdf, p 13

4.3 Review Strategy

4.3.1 Materials Consulted during Medical Review

The following materials were consulted during the conduct of this review:

- NDA 21-873; Submission Date of December 22, 2004
- NDA 21-873 4-Month Safety Update; Submission Date of April 29, 2005
- Minutes of all regulatory meetings and telephone conferences with the Applicant that were contained in Division files
- Applicant responses to FDA queries, submitted March 7 and October 17, 2005 and January 3, January 4 and January 6, 2006

4.3.2 Review Processes and Procedures

The clinical review was based on the medical officer's review of the material delineated above and supplemented by the reviews conducted by Chemistry, Clinical Pharmacology, Pharmacology/Toxicology and Statistics. A consult was obtained from the Division of Scientific Investigations (DSI). The Division of Drug Marketing, Advertising and Communication (DDMAC), Division of Medication Errors and Technical Support (DMETS), and the Division of Surveillance, Research and Communication Support (DSRCS) provided comments about the proposed trade name and labeling (see Section 8.8).

4.3.3 Materials Reviewed

The review conducted by this medical officer focused on the two pivotal randomized clinical trials comparing DRSP/EE to placebo for efficacy in managing symptoms associated with PMDD, and safety, particularly with regard to changes in serum electrolytes and risk of venous thromboembolic events (VTEs). All materials submitted on December 22, 2004, in electronic format for these studies were considered during the conduct of this review. Additionally, safety update material submitted on April 29, 2005, which provided the updated reports on eight US and foreign phase 1 and 3 studies evaluating DRSP 3 mg/EE 20 µg, including one of the two pivotal studies (Study 304049) over the reporting period February 14, 2004 to February 22, 2005.

4.4 Data Quality and Integrity

During a monitoring visit pertaining to Study 305141, it was discovered that one site (_____) had numerous CRFs and Data Correction Forms on which the subinvestigator's signature was forged by the study coordinator. The coordinator had also forged three informed consent forms where the originals had been misplaced, although the original consent files, with proper subject signatures, were later found. In addition, the study coordinator had failed to collect the subject diaries from all subjects at the end of treatment. Within days of this discovery, the coordinator was terminated, and the IRB was notified. Berlex Clinical Research Associates conducted a complete check on all source documentation for both trials at this site.

Seven subjects, three of whom completed the trial, were enrolled at this site. Attempts were made to retrieve all diaries and to confirm that the entries were appropriately made by the subjects. One subject (#120031, placebo→DRSP/EE) had previously admitted to asking her daughter to complete her diaries for her several weeks after the fact, without any attempt to reconstruct her status at the time. This subject was removed from the Per Protocol analysis. Of the remaining six, one (#120007) did not return any diaries. Four subjects returned their diaries and confirmed that the entries were their own. One (#120020), who had withdrawn during TP1 and who only had baseline DRSPS scores) was unable to be contacted. In addition to subject #120031, subjects #120007 and 120020 were removed from the Per Protocol analysis.

Further review of this site for Study 304049 also found some discrepancies and apparent forgeries. One of three subjects randomized at that site indicated that diary entries appeared not to be in her own handwriting (#860015). Her data were excluded from the Per Protocol analysis. The other two subjects confirmed that all diary data were self-recorded; however, one of these subjects (#960007) had withdrawn consent before concluding the study, and had not submitted any treatment diary data.

Medical Reviewer's Comment:

- **A total of ten subjects, seven from Study 305141 and three from Study 304049, were randomized at the site where misconduct was discovered. Two subjects withdrew prior to submitting any treatment cycle data, and therefore were not included in the Full Analysis set. One subject had already been removed from the Per Protocol set due to her own fraudulent submission. Five subjects confirmed that their data were accurate and in their own hand. The remaining two subjects were removed from the Per Protocol population; one had not submitted any diary data and one was unable to be contacted. Therefore, it appears that only two subjects (#120031 in Study 305141, and #860015 in Study 304049) might potentially have fraudulent data in the Full Analysis set. Since the Per Protocol results were confirmatory of the Full Analysis results, there is not believed to be any adverse impact of this study misconduct on the validity of the study results.**
- **At the FDA's request, the Applicant provided a reanalysis of the data excluding all subjects from this site in both studies. For Study 304049, of the three subjects**

randomized, one DRSP/EE subject was not included in the original modified ITT analysis due to lack of postbaseline luteal phase data. Therefore, the data set as reanalyzed omitted a single subject each from the DRSP/EE and placebo groups. The difference between treatment arms in change from baseline was minimally different from the original analysis (-7.3, as compared to -7.5) and remained significant ($p=0.0002$). In Study 305141, of the seven subjects randomized, four (three in the DRSP/EE→placebo group, one in the placebo→DRSP/EE group) had no postbaseline data, and therefore were not included in the original modified ITT analysis. As reanalyzed, the data set omitting subjects from this site omitted one DRSP/EE→placebo subject and two placebo→DRSP/EE subjects. The difference between treatment arms was unchanged (-12.5) and remained significant ($p=0.0007$).

Inspections by the Division of Scientific Investigations (DSI) were requested on two study sites, based on the sites' contributions to the overall subject pool. The two investigators audited were Drs. Moreines and Drosman; the latter site contributed subjects to both of the clinical trials. Dr. Moreines had enrolled 15 subjects, 11 of whom completed the trial. The audit concluded that this site had adhered to applicable statutory requirements and FDA regulations. Dr. Drosman enrolled 40 subjects who completed Study 304049 and 14 who completed Study 305141. A form 483 notice of violation was issued, but only a "voluntary action indicated" notice was issued. Deficiencies included delayed assessment of adverse events and assessment by personnel other than the investigator, use of expired pregnancy test kits, and physical exams performed by a practitioner not included on Form 1572. However, the DSI consult recommended that the data submitted by Dr. Drosman appear adequate to support the NDA. It was recommended that the medical reviewer determine whether a subject on a daily antibiotic regimen, who was not excluded from analysis, should be excluded.

Medical Reviewer's Comment:

- **Subject #840069, assigned to placebo in Study 304049 used a daily regimen of tetracycline, and was included in both the Full Analysis and Per Protocol analysis sets. The reviewer does not object to inclusion of this subject's data in the analysis.**

4.5 Compliance with Good Clinical Practices

Berlex Laboratories was responsible for quality assurance audits at clinical study sites in both trials. Both studies were monitored regularly by Clinical Research Associates to ensure compliance with Good Clinical Practice (GCP). Laboratory analysis in both studies was performed by a central laboratory, Covance.

4.6 Financial Disclosures

The applicant submitted financial disclosure statements for investigators who participated in the two pivotal phase 3 trials (Studies 049 and 141). This information was reviewed as part of the clinical review, and it was concluded that for all 37 investigators in Study 049 and all 9 investigators in Study 141:

- the information was complete
- appropriate documentation was received
- the information complied with 21 CFR 54
- no disclosable information was reported
- no conflicts of interests were noted
- there was no disclosure of financial interests that could bias the outcome of the trials

Medical Reviewer's Comment:

- **Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of either of the pivotal trials for NDA 21-873.**

5 CLINICAL PHARMACOLOGY

The Human Pharmacokinetics and Bioavailability section of NDA 21-873 was cross-referenced to NDA 21-676. The initial submission of NDA 21-676 for the oral contraceptive indication was found acceptable by the Clinical Pharmacology reviewer in 2004.

5.1 Pharmacokinetics

No new pharmacokinetics studies were submitted in NDA 21-873; studies from NDA 21-676 were cross-referenced.

5.2 Pharmacodynamics

No new pharmacodynamics studies were submitted in NDA 21-873; studies from NDA 21-676 were cross-referenced. The threshold dose for ovulation inhibition was determined to be 2 mg DRSP per day in a 21-day treatment regimen.

5.3 Exposure-Response Relationships

No new clinical pharmacology studies were submitted in NDA 21-873; studies from NDA 21-676 were cross-referenced.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication studied in this NDA is a secondary indication for "treatment of symptoms of premenstrual dysphoric disorder (PMDD) who have no known contraindications to oral contraceptives and who desire contraception." (sic).

Medical Reviewer's Comment:

- **The indication should be amended to read: "treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who chose to use an oral contraceptive as their method of contraception."**

6.1.1 Methods

Data from two pivotal phase 3 randomized, comparator-controlled trials, Studies 304049 and 305141, were submitted and reviewed in support of the proposed indications.

6.1.2 General Discussion of Endpoints

The eight instruments used to assess efficacy in both trials are summarized in Table 2.

Table 2 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

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 (see Table 3). 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.

**APPEARS THIS WAY
 ON ORIGINAL**

Table 3 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:	
<ul style="list-style-type: none"> • 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

DRUP had requested at the October 2004 pre-NDA meeting that the Applicant provide information regarding the validation of the DRSPS. The DRSPS was initially developed to assist clinicians in assessing the DSM-IV criteria for PMDD. The Applicant noted that the DRSPS has been used in several of the published trials of SSRIs for PMDD, and presented a now-published manuscript⁴ reporting on two studies conducted to assess the reliability and validity of the instrument. One trial, with N=27, included women with a wide range of premenstrual symptomatology, including none. The second trial, with N=243, enrolled women who had met DSM-IV criteria for PMDD over two menstrual cycles, and had presented for treatment. Internal consistency and test-retest reliability of the DRSPS (24 items) were assessed in the two studies. Concurrent validity of the DRSPS was assessed against late luteal phase ratings on the Hamilton Depression Rating Scale, 21 item version in the small study. In the larger study, in the PMDD population, concurrent validity of the DRSPS 21 item scale and of the three functional items was assessed against the Hamilton Depression Rating Scale, the Social Adjustment Scales and the Q-LES-Q. Reliability in both studies was good, particularly for late luteal phase measurements. Correlations with other instruments in the PMDD population were in the moderate range. Sensitivity to change with treatment was also demonstrated in the PMDD population, particularly in the Summary Scores as opposed to the individual items.

Medical Reviewer's Comment:

- **While not certain that criteria such as those recommended by the FDA's Study Endpoints and Labeling Division for demonstrating validity of an instrument have been met, the reviewer concurs that the DRSPS is a reasonable and useful instrument to use for the assessment of the primary efficacy endpoint. Its use in studies of other approved PMDD treatments facilitates comparison of the current study results with the outcomes of SSRI treatments.**

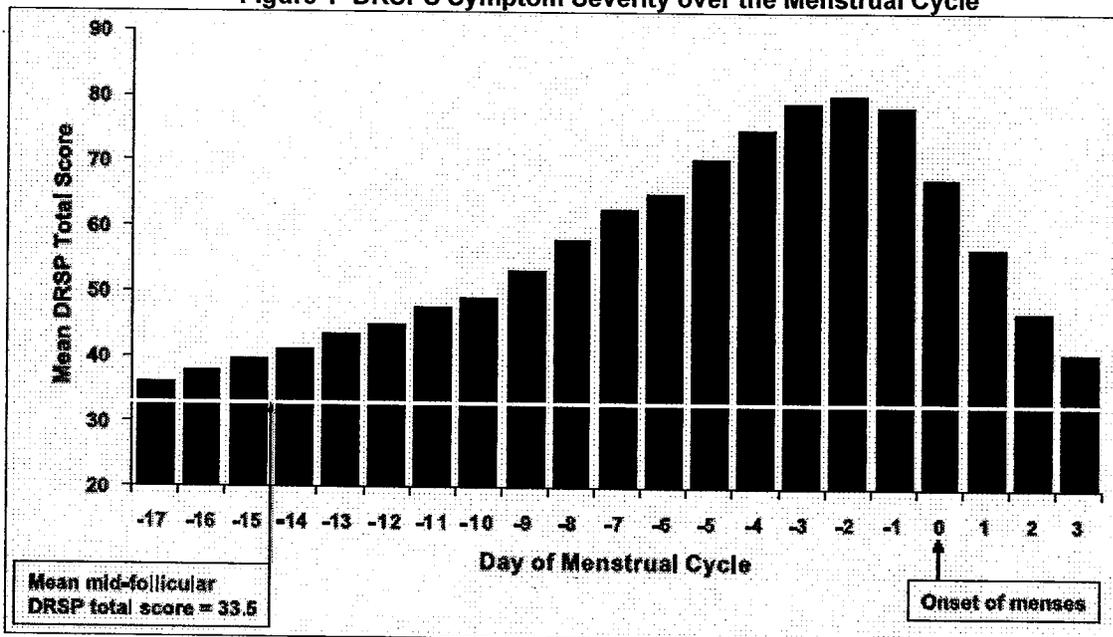
The primary efficacy endpoint was the change from baseline in the average over three treatment cycles of the first 21 items of the DRSPS. For each cycle, each of the first 21 items was averaged over the five days preceding menses, and the averages were then summed. The primary efficacy variable was the 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.

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 and reported the analysis of data over the five days preceding menses.

Medical Reviewer's Comment:

- **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 study⁵ 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 1).**

Figure 1 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

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 and DRSPS values for these days were used in the analyses. 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. Similarly, if two consecutive days had a missing item, the item could not be imputed. If more than two days of an item were missing after the above imputation was done, the item average was set as missing. If the average of any of the 21 DRSPS items were missing for a given cycle, the DRSPS score for that cycle was set to missing. The overall on-treatment DRSPS score was averaged over the number of cycles with available data (and weighted according to the number of cycles contributing data).

Medical Reviewer's Comment:

- ***The use of the DRSPS as the primary endpoint instrument was agreed to by DNDP, although 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.***
- ***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 in both trials.***
- ***DNDP had recommended that missing data be imputed by averaging all non-missing data points for that cycle; instead the Applicant has averaged only the two bordering days' data. However, in each cycle in Study 304049, 94-95% of subjects had no imputed scores. In Study 305141, in TP1, 92% of DRSP/EE→placebo subjects and 89-90% of placebo→DRSP/EE subjects in each cycle had no imputed scores, and in TP2, 89-94% of DRSP/EE→placebo subjects and 100% of placebo→DRSP/EE subjects in each cycle had no imputed scores. It is therefore unlikely that this difference in methodology had a notable effect on the results.***
- ***In addition, both the DNDP and DRUP statistical reviewers, in reviewing the Statistical Analysis Plan, had expressed concern that the proposed rule for handling missing data could result in exclusion of a subject who received medication, and had at least one post-randomization measurement from the ITT population. The Applicant was asked to clarify and refine this rule, to propose sensitivity analyses to verify the robustness of the data obtained, and to provide an overall summary of missing data observed. In fact, according to the Applicant's response of January 6, 2005 to a DRUP inquiry, it appears that in fact, "subjects who took at least one dose of study drug but discontinued participation prior to recording sufficient data at the luteal phase for Treatment Cycle 1 were not included in the efficacy analyses."***

The three functional items of the DRSPS were evaluated as secondary endpoints. Additional secondary endpoints were based on the Clinical Global Impressions scale (CGI), the Short Form-36 (SF-36), the Endicott Quality of Life Enjoyment and Satisfaction questionnaire (Q-LES-Q), and the Premenstrual Tension Syndrome scale (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 [one treatment cycle in each treatment period in Study 305141]) was also used to analyze the primary efficacy variable. Table 4 displays the analysis populations in each study, as a percent of the total number of subjects enrolled.

Table 4 Number of Subjects in Analysis Sets by Treatment and Study

Study	Analysis Set	N (%)	N (%)
304049		DRSP/EE N=232	Placebo N=218
	Full Analysis	231 (99.6%)	218 (100%)
	Per Protocol	158 (68.1%)	166 (76.2%)
305141		DRSP/EE N=34	Placebo N=30
	Full Analysis	34 (100%)	30 (100%)
	Per Protocol	12 (35.3%)	10 (33.3%)

Source: Text Tables 6 & 19, ise.pdf, pp 36 & 53

Medical Reviewer's Comment:

- *As noted in the previous comment, 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 (mITT) population. In Study 304049, 41 DRSP/EE subjects and 23 placebo subjects were excluded on this basis, and in Study 305141, seven DRSP/EE→placebo subjects and six placebo→DRSP/EE subjects were excluded. (An additional subject in each sequence completed the study but did not provide any diary data.)*
- *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.*

6.1.3 Study Design

Protocol 304049

Protocol 304049 was a phase 3, U.S. multicenter, randomized, double-blind, placebo-controlled three month treatment duration study designed to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in the treating symptoms of PMDD. Subjects diagnosed with PMDD by DSM-IV criteria were enrolled in a treatment phase lasting three menstrual cycles following a two cycle run-in phase. 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.

Protocol 305141

Protocol 305141 was a phase 3, U.S. multicenter, randomized, double-blind, placebo-controlled crossover study, also designed to evaluate the clinical efficacy and safety of DRSP/EE as compared to placebo in 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, and 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.**
- **DRUP had expressed concerns about the decision to terminate enrollment prematurely for Study 305141, both in terms of the adequacy of the sample size, and the possibility of bias due to the early discontinuation. The Applicant noted that difficulty in recruitment and budgetary constraints had mandated the early termination of enrollment. At the time the decision was made, only three subjects had completed the entire treatment sequence, and only four of the 37 subjects who had completed Cycle 1 of TP1 had submitted their diaries. In addition, the study remained blinded until the database lock.**
- **The reviewer agrees that early knowledge of treatment results does not appear to have influenced the decision to terminate enrollment in Study 305141.**

In both studies, the population studied was women with PMDD diagnosed by the DSM-IV criteria, as observed over two menstrual cycles. Inclusion and exclusion criteria were similar in the two studies:

Inclusion Criteria

- PMDD by DSM-IV criteria (see Table 25)
 - At screening, by history
 - At the end of the second run-in cycle, by review of symptom records
- Any 5 distinct items, without overlap (i.e., two items with the same number, such as 1a and 1c, cannot be counted as two distinct items), on the DRSPS (see Table 3) (each of the 2 consecutive baseline run-in cycles must have fulfilled the following criterion):
 - Luteal phase daily average score of ≥ 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 diary must have been present for at least 3 of these days for the item to be used as an inclusion criterion for that month (i.e., for comparison with luteal phase score as below).

- 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 Structured Clinical Interview for DSM-IV (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 age of 34 years 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
- Known 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, carbamazepine, 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 \geq 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 Comments:

- *There were no important differences between treatment groups at baseline in either study.*

6.1.4 Efficacy Findings

Study 304049

For Study 304049, Table 5 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.

Table 5 DRSPS Score & Change from Baseline by Treatment Group and Cycle (Study 304049)

	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

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 FDA requested that the Applicant provide a sensitivity analysis, to assess the impact of the exclusion of subjects from the mITT population who met the definition of the Full Analysis set, but did not have luteal phase data post-baseline. This analysis was done by determining the mean percent change from baseline in DRSPS score for the placebo group, and applying this percent change to the baseline score of each Full Analysis subject who received DRSP/EE and was excluded from the mITT population. This imputation was done only for the first cycle of treatment, so in the ANCOVA of weighted change scores, the imputed scores were weighted by one cycle. The reanalysis had the effect of adding 41 DRSP/EE subjects. The ANCOVA results changed very little. The improvement overall among DRSP/EE subjects was 6.6 points greater (compared to 7.5 points in the mITT population), and the significance level was 0.0002.**

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 Comment:

- **The magnitude of the difference in treatment response between arms at the first cycle suggests that the efficacy results in Study 304049 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

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 one 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.***

Study 305141

In both the DRSP/EE→placebo and placebo→DRSP/EE groups, the decrease from baseline to the average of the three cycles of TP1 was statistically significant ($p < 0.0001$ for DRSP/EE→placebo; $p = 0.0001$ for placebo→DRSP/EE sequence). The decrease from washout to the average of the three cycles of TP2 was statistically significant in the placebo→DRSP/EE sequence ($p = 0.0005$) and the increase from washout in the DRSP/EE→placebo group was of marginal significance ($p = 0.0664$). Table 6 displays these results.

Table 6 DRSPS Score & Change from Baseline by Treatment and Cycle

	Statistic	Run-in 1 & 2 average	Cycle 1	Cycle 2	Cycle 3	Cycle 1-3 average
DRSP/EE	N	26	26	26	25	26
	Mean (SD)	71.3 (17.7)	-33.5 (23.6)	-32.8 (20.1)	-36.3 (20.6)	-34.0 (18.3)
	Change from baseline p value		<0.0001	<0.0001	<0.0001	<0.0001
Placebo	N	23	23	20	18	23
	Mean	69.8 (13.5)	-19.7 (26.0)	-21.4 (26.6)	-19.3 (18.6)	-19.9 (20.8)
	Change from baseline p value		0.0015	0.0019	0.0004	0.0001
	Between-group p value	0.71				
	Statistic	Washout Cycle	Cycle 4	Cycle 5	Cycle 6	Cycle 4-6 average
DRSP/EE	N	16	16	12	9	16
	Mean	57.5 (23.3)	-16.1 (13.0)	-10.1 (23.3)	-25.8 (22.9)	-17.0 (15.4)
	Change from baseline p value		<0.0002	0.162	0.010	0.0005
Placebo	N	18	18	15	14	18
	Mean	40.0 (14.3)	8.2 (16.5)	4.5 (19.9)	8.9 (24.7)	7.5
	Change from baseline p value		0.049	0.399	0.198	0.066
	Between-group p value	0.006				

Source: Tables 14, a07545.pdf, Section 14, pp 155-6

The Applicant's ANCOVA analysis of mean change from baseline by treatment group in Study 305141 pooled the DRSP/EE treatment groups from TP1 and TP2 and pooled the placebo groups from TP1 and TP2, using the effect of treatment order as a factor. The ANCOVA comparing the difference between the two drug exposures in the adjusted mean change from baseline averaged over the three treatment cycles found that the improvement on DRSP/EE was 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by subjects while taking placebo ($p=0.0001$). The advantage for DRSP/EE was slightly greater (16.1 points, confidence limits 7.9 to 24.4), with a p -value of 0.0006, when analyzed using the per protocol population.

Medical Reviewer's Comments:

- **The FDA statistician reanalyzed the data looking at the effect of each treatment assignment in each treatment period. Her results demonstrated a statistically significant difference between DRSP/EE and placebo with a change from baseline of -14 (95% CI -25 to -3, $p=0.02$) for TP1 and of -24.5 (-36 to -13, $p=0.001$) for TP2.**
- **A statistically significant difference between treatment arms, favoring DRSP/EE was seen for the primary efficacy variable, change from baseline on the DRSPS score. This finding held both for the Applicant's analysis, which collapsed treatment assignments over treatment periods, and for the FDA analysis, which analyzed the difference between DRSP/EE and placebo at each treatment period.**
- **A sensitivity analysis, as described above for Study 304049, was also conducted for Study 305141, to assess the impact of excluding subjects without luteal phase data from the Full Analysis set. This had the effect of adding eight DRSP/EE to the TP1 analysis, and three DRSP/EE subjects to the TP2 analysis. The ANCOVA results changed very little. The improvement from baseline overall among DRSP/EE subjects was 12.39 points greater than that seen in the placebo group (compared to 12.45 points in the mITT population), and the significance level was 0.0002. When the data were imputed in this manner and analyzed only over TP1, the difference between DRSP/EE and placebo in change from baseline was -11.23 ($p=0.011$).**

The Applicant again conducted the analysis of efficacy at the first cycle of treatment, showing that the difference between DRSP/EE and placebo at Cycle 1 in Study 305141 (difference at Cycle 1 collapsed over both treatment periods) of -12.4 was statistically significant ($p=0.02$). Results obtained by the FDA statistician, who reanalyzed the data looking at the effect of each treatment assignment in each treatment period, demonstrated a statistically significant difference between DRSP/EE and placebo in change from baseline at the first treatment cycle of -14 (95% CI -25, -3, $p=0.02$) for TP1 and of -24.5 (-36, -13, $p=0.001$) for TP2.

Medical Reviewer's Comment:

- **The most relevant assessment of effect at first cycle is the FDA statistician's analysis of Cycle 1 in TP1, since, if unblinding did occur due to changes in menstrual bleeding profiles, this would be evident at TP2. The difference in treatment response between arms at the first cycle in TP1 suggests that the efficacy results in Study 305141 were not attributable to a possible compromise in blinding.**

6.1.5 Clinical Microbiology

This section is not applicable, as this product is not an antimicrobial nor is it administered parenterally.

6.1.6 Efficacy Conclusions

In the primary efficacy analysis for both studies, 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.

In Study 304049, 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. Due to concerns about the impact of potential loss of blinding on the efficacy findings, 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 in both studies, showing that the difference between DRSP/EE and placebo at Cycle 1 in Study 304049 of -8.2 was statistically significant ($p=0.0002$). 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.

In Study 305141, the ANCOVA results submitted by the Applicant, which collapsed treatment assignment over treatment period, demonstrated a statistically significant difference between DRSP/EE and placebo groups in the adjusted mean change from baseline averaged over the three relevant treatment cycles, with the improvement in the DRSP/EE group 12.5 points greater (95% confidence limits 6.7 to 18.3) than that experienced by placebo subjects ($p=0.0001$). Results were similar, with $p=0.006$, when analyzed using the per protocol population.

The Applicant again conducted the analysis of efficacy at the first cycle of treatment, showing that the difference between DRSP/EE and placebo at Cycle 1 in Study 305141 (difference at Cycle 1 collapsed over both treatment periods) of -12.4 was statistically significant ($p=0.02$). Results obtained by the FDA statistician, who reanalyzed the data looking at the effect of each treatment assignment in each treatment period, demonstrated a statistically significant difference between DRSP/EE and placebo in change from baseline at the first treatment cycle of -14 (95% CI -25, -3, $p=0.02$) for TP1 and of -24.5 (-36, -13, $p=0.001$) for TP2.

In both studies, 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), in both trials
- Change from baseline in the interviewer-rated global improvement scale of the CGI in both trials, along with two other scores (severity of illness and efficacy index) in Study 305141
- Change from baseline in the total score of the first 14 items, and the score of overall life satisfaction, on the Q-LES-Q in Study 305141
- Change from baseline in the PMTS observer and self-rated scales, in both studies

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 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 close relationship to the primary endpoint, and due to their utility in assessing the effects of treatment on social and professional functioning.

No effect on weight was seen in either trial.

In the pre-NDA meeting, DRUP 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. The Applicant addressed this request by several means.

First, the Applicant notes that evidence of clinically meaningful change in psychiatric conditions may be determined by change in health status from dysfunctional to functional. Citing two literature studies^{6,7}, the Applicant notes that mean DRSPS scores for items 1-21 were markedly higher in women empirically categorized as having PMDD (63%, 50% and 22%, respectively) as compared to those categorized as minimal, moderate or severe premenstrual syndrome (PMS). In the second study, women with severe PMS were more likely to display functional impairment than were women with moderate PMS. The difference in mean DRSP score between moderate to severe PMS was estimated as 28%. Therefore, the Applicant proposes that a change in DRSP score of 28-50% represents a clinically meaningful change in premenstrual symptomatology, incorporating elements of patient-ratings of symptoms, health-related quality of life measures, and impairment and occupational productivity as well as objective ratings of absenteeism, health care utilization and health care costs.

The data from the two PMDD trials also were analyzed by a responder analysis, with response defined as a reduction of $\geq 50\%$ in DRSP scores. The responder rates were 48.4% for DRSP/EE subjects vs. 36.1% for placebo subjects in Study 304049, and 42.9% for DRSP/EE subjects vs. 19.5% for placebo subjects in Study 305141.

Medical Reviewer's Comment:

- ***The reviewer is not convinced that the data obtained from several unrelated studies, using cross-sectional methodologies, create a logical chain of evidence supporting the proposition that a reduction of 50% in DRSPS score constitutes a clinically meaningful improvement.***

Secondly, the Applicant states that confirmatory evidence of statistically significant improvement on secondary endpoints, particularly those relevant to function and global improvement, support the clinical relevance of the primary outcome measure.

Medical Reviewer's Comment:

- ***The reviewer concurs that a number of the secondary endpoints support the efficacy findings of the primary endpoint.***

Thirdly, the Applicant estimated the MICD using a distribution-based method, which utilizes a calculated effect size which is independent of the specific measurement instrument used. Effect sizes are used to compare results across studies which may use different instruments. The effect size is calculated by dividing the mean difference in response between treatment and placebo groups by the corresponding standard deviation (SD). By convention¹, effect sizes of 0.2, 0.5 and 0.8 SD units represent small, medium and large treatment effects. The Applicant presented the effect sizes for the two studies in a whisker plot (see Figure 2); the values were obtained for each study by dividing the mean difference between DRSP/EE and placebo in change from baseline on the 21 items of the DRSPS by the standard deviation of the pooled average baseline scores. Similarly, the pooled effect sizes for the published SSRI

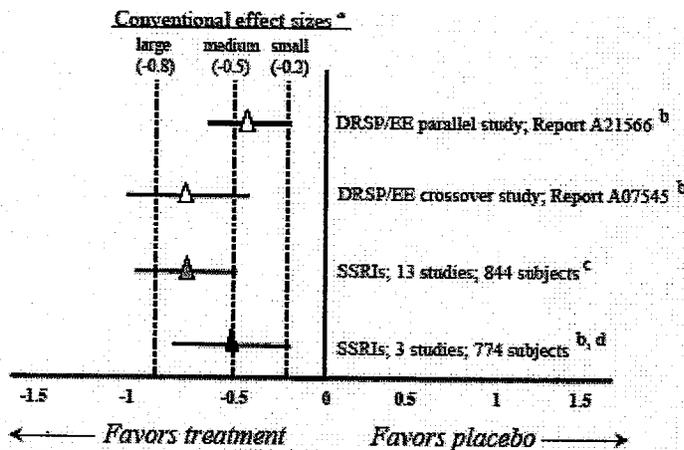
studies (13 general studies and 3 studies using the DRSPS as outcome measure) were computed by dividing the published mean difference between treatment and placebo, by the baseline standard deviation.

By this measure, the effect sizes demonstrated for treatment with DRSP/EE is in fairly close approximation to the effect sizes calculated from pooled data from published trials of SSRIs.

Medical Reviewer's Comment:

- **The reviewer finds the comparison of effect size to that observed in trials of SSRIs relevant and concurs that the effect size is similar for the two types of treatment of PMDD.**

Figure 2 Effect Size of DRSP/EE vs. SSRIs for Treatment of PMDD



DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg; PMDD = premenstrual dysphoric disorder; SD = standard deviation; SSRIs = selective serotonin re-uptake inhibitors.

^a Conventional effect sizes suggested by Cohen. (14)

^b DRSP instrument used to measure outcome.

^c Various instruments used to measure outcome from the pooled data of 13 clinical trials.

(16)

^d Pooled data from 3 clinical trials. (4, 6, 7)

Effect size is calculated by difference in score between active drug and placebo control group divided by the corresponding SD.

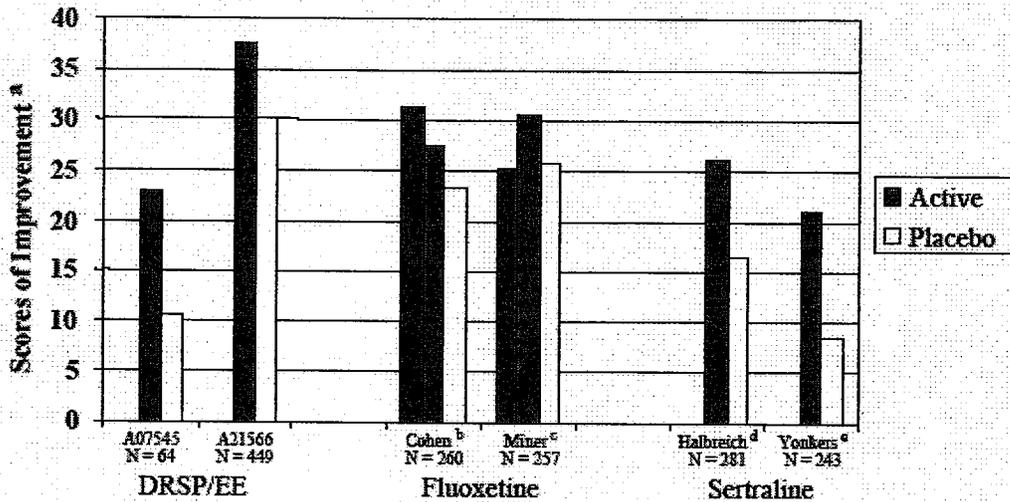
Source: Text Figure 3, ise.pdf, p 76

Finally, the Applicant provides a figure comparing the absolute change from baseline in treatment vs. placebo groups for DRSP/EE and for published trials of fluoxetine and sertraline (see Figure 3).

Medical Reviewer's Comment:

- **The absolute change in the DRSP/EE trials, particularly in the more robust Study 304049 (listed in the figure as A21566), 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 trials, supporting the proposition that the treatment benefit of DRSP/EE is similar to that for approved SSRI treatments for PMDD.**

Figure 3 Absolute Change from Baseline in Treatment and Placebo Groups



DRSP = Daily Record of Severity of Problems scale; DRSP/EE = drospirenone 3 mg/ethinyl estradiol 0.02 mg; N = total number of subjects in the study; PMDD = premenstrual dysphoric disorder; SSRI = selective serotonin re-uptake inhibitor.

^a Scores of improvement = absolute mean change

^b Dosage = 10 mg daily (on left); 20 mg daily (in middle) (7)

^c Dosage = 90 mg 7 days before menses (on left); 90 mg 14 and 7 days before menses (in middle) (5)

^d Dosage = 50 - 100 mg daily (6)

^e Dosage = 50 - 150 mg daily (4)

Source: Text Figure 4, ise.pdf, p 78

The reviewer also turned to the reviews of the original NDA submissions for the three SSRIs approved for the PMDD indication to attempt a comparison of the DRSP/EE results to those attained by the SSRIs. A number of NDAs have been submitted for SSRIs seeking approval for 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. Comparative results from the various SSRI trials and from the two DRSP/EE trials are shown in Table 7.

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 Lisa M. Soule, M.D.
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 YAZ, Drospirenone/Ethinyl Estradiol
 Final Jan 20, 2006

Table 7 Comparative Results from SSRI Trials and DRSP/EE Trial

Drug/Trial/Exposure Treatment Group (N)	Outcome Measure	
NDA 21-873, DRSP/EE	% change from baseline in DRSPS 21, averaged over 3 treatment cycles	Actual change from baseline in DRSPS 21, averaged over 3 treatment cycles
Study 304149		
Placebo (190)	-38% (30/78.1 Table 18)	-30
DRSP/EE (194)	-48% (37.5/77.4)	-37.5 (p=0.0001)
Study 305141		
TP1: Placebo (23)	-29% -20/70 (Table 14)	-20
TP1: DRSP/EE (26)	-48% -34/71	-34 (p=0.02)**
TP2: Placebo (16)	+19% 7.5/40	+7.5
TP2: DRSP/EE (18)	-30%*** -17/57.5	-17 (p=0.001)**
NDA 18-936, S-058 (Fluoxetine continuous dose)	% change from baseline in VAS Mood-3, averaged over 6 treatment cycles	
Placebo (94)	-6%	
Fluoxetine 20 mg (95)	-37% (p=0.002)*	
Fluoxetine 60 mg (85)	-43% (p=0.002)*	
NDA 18-936, S-067 (Fluoxetine luteal phase dose)	% 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 19-839, S-039 & 20-990, S-007 (sertraline tablet and oral concentrate for continuous or luteal phase dosing)		Actual change from baseline in DRSPS 24, averaged over 3 treatment cycles
Study 256 (continuous dosing)		
Placebo (106)		-9.6
Sertraline# (104)		-25.1 (p=0.0001)
Study 493 (luteal phase dosing)		
Placebo (110)		-16.0
Sertraline#(119)		-24.7 (p=0.002)

NDA 20-936, SE1-011 (paroxetine CR continuous dosing)	%change from baseline in VAS Mood-4, at 3 rd treatment cycle
Study 677	
Placebo (79)	-43%
Paroxetine 12.5 mg/day (67)	-64%
Paroxetine 25 mg/day (70)	-67%
Study 688	
Placebo (86)	-58%
Paroxetine 12.5 mg/day (94)	-65%
Paroxetine 25 mg/day (85)	-64%
Study 689	
Placebo (95)	-47%
Paroxetine 12.5 mg/day (92)	-64%
Paroxetine 25 mg/day (78)	-67%

*p-value based upon actual change from baseline; values not reported here since they would not be comparable to DRSP/EE results, given the use of a different instrument

**based on results calculated by FDA statistician

***"baseline" in TP2 is the washout cycle, or average of the two run-in cycles if washout data missing

#dose titrated up as needed from 50 mg; mean dose in completers 102 mg/day (Study 256), 74 mg/day (Study 493)

The review of the fluoxetine continuous dosing application, of 12/14/99 by Dr. Thomas Laughren of DNDP recommended nonapproval, due to significant methodological problems in one of the three trials submitted, all of which were identified by the Applicant through review of the published literature. The most robust trial was a six-cycle study that used the VAS Mood-3 as the outcome measure. While this measure cannot be equated to the DRSPS, comparison of the treatment effect, in terms of percent change from baseline is of interest.

These results, contrasted with similarly calculated treatment effects for DRSP/EE show similar levels of efficacy for the study drug, as measured by percent change from baseline (37-43% in the fluoxetine trials, vs. 30-48% in the DRSP/EE trials), although the placebo effect is considerably higher in the DRSP/EE trials.

The review of 12/15/01 by Dr. Laughren for fluoxetine luteal phase dosing focused on the primary endpoint measured by the DRSPS, first 21 items – thus, directly comparable to the outcome in the DRSP/EE trials. On-treatment scores were averaged over the three treatment cycles, as in NDA 21-873. Here, the placebo response is equivalent to that seen in the DRSP/EE trials, 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.

Submissions for sertraline continuous and luteal phase dosing were reviewed by Dr. Laughren on November 4, 2001, resulting in a recommendation for an approvable action pending acceptable labeling. Two studies were submitted, one conducted by an academic group outside of an IND. This study used all 24 items on the DRSPS as the endpoint, which makes it difficult to directly equate the results to the DRSP/EE studies. However, the differences between study drug and placebo in change from baseline (15.5 and 8.7) are only slightly greater than those seen in the DRSP/EE trials, and, if adjusted for the number of DRSPS items evaluated, the adjusted differences (13.6 & 7.6) are almost identical to that seen in the DRSP/EE trials (7.5 for Study 304049; 14 and 9.5 for Study 305141).

Paroxetine controlled release (CR) received a recommendation for an approvable action from Dr. Karen Brugge on 12/31/02, based upon analysis of a DNDP-requested primary endpoint, the VAS-Total Score, rather than the Applicant-designated endpoint, the VAS-Mood 4 score over three cycles. The difference

in percent change from baseline between placebo and study drug ranged from 6-24% over three trials and two dose levels, as compared to a difference of 10-19% in the two DRSP/EE trials.

Finally, an NDA for paroxetine CR for luteal phase dosing was reviewed by Dr. Paul Andreason on January 21, 2004. The endpoint in the three-cycle trial was the VAS-Mood Score, with the treatment endpoint being the score at treatment cycle 3. However, since only change from baseline (not actual score at baseline and at cycle 3) is reported, percent change cannot be calculated for comparison to the DRSP/EE trials.

Thus, the most relevant comparison to results obtained with DRSP/EE is with the fluoxetine luteal phase trial, which used the identical outcome measure, over the same treatment period. The placebo responses were -23 for fluoxetine, vs. -30 for Study 304049 and -20 for Study 305141 at TP1, and +7.5 at TP2, where response might have been affected by treatment sequence and by the differing baselines as measured at washout. The active study drug responses were -28 to -31 depending on fluoxetine dose, compared to -37.5 for DRSP/EE in Study 304049 and -17 to -34 for DRSP/EE in Study 305141, depending on treatment sequence. 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 Study 304049, and 9.5 to 14 for Study 305141). This treatment effect was judged to provide adequate evidence of efficacy for the SSRI, 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 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.

Medical Reviewer's Comments:

- **Given the Applicant's use of the washout cycle score as the baseline to which TP2 scores were compared, obtaining the TP2 baseline with the prior drug's effect carrying over would result in subjects who were switching from DRSPS/EE to placebo having a lower baseline DRSPS score, thus making it more difficult to demonstrate improvement from baseline in TP2 for the placebo subjects. This would result in a larger difference between DRSP/EE and placebo in change from baseline for TP2.**
- **However, both the results at 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 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. 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.

Medical Reviewer's Comments:

- **The reviewer concurs that the results of Studies 304049 and 305141 provide evidence of the efficacy of DRSP/EE in treating symptoms of PMDD.**

7 INTEGRATED REVIEW OF SAFETY

All 285 participants who received at least one dose of study medication were included in the summaries and listings of safety data (N=231 for Study 304049, N=54 for Study 305141). 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. In both studies, a pretreatment adverse event that worsened in intensity over the course of treatment was considered treatment-emergent. In Study 305141, those adverse events occurring in the wash-out period were attributed to the drug received in the preceding treatment period. Adverse events were coded according to the Hoechst Adverse Reaction Terminology System (HARTS) dictionary and were summarized by body system and preferred term.

The following safety measurements were evaluated:

- Physical and gynecological examinations and Pap smears
- Vital signs
- Laboratory assessment (hematology, serum chemistries including sodium and potassium levels, thyroid, hepatic and lipid panels, and urinalysis)
- In addition to adverse events generally, selected cardiovascular (arrhythmia, brady/tachycardia, dizziness, palpitations and syncope that might be related to alterations in serum potassium) and thromboembolic events were evaluated

Laboratory measures were assessed by summary statistics at baseline (Visit 3), start of treatment Cycle 2 (Visit 5) and end of treatment (EOT, Visit 7), as well as at the washout and Cycle 5 visits in Study 305141. 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 ≥ 5.5 mEq/L was tabulated by treatment, and the proportions in each category compared between treatment arms.

Summary statistics were presented for vital signs measurements at each visit and for change from baseline (Visit 4) to Cycle 2 and EOT.

7.1 Methods and Findings

Safety data from the two pivotal phase 3 trials were reviewed. A safety update was submitted on April 29, 2005; data from this update were incorporated into the safety review.

7.1.1 Deaths

There were no deaths in either of the trials.

7.1.2 Other Serious Adverse Events

There were a total of five serious adverse events (SAEs) in the two trials (see Table 8). Three occurred in subjects randomized to DRSP/EE in Study 304049: incarcerated incisional hernia, abnormal Pap and spinal bone spurs. Two occurred in subjects taking placebo (one in each trial): appendicitis and miscarriage following a pregnancy diagnosed during the placebo exposure period. The overall rates of SAEs in the two exposure groups were therefore 1.1% in the DRSP/EE-exposed subjects and 0.7% in the placebo-exposed subjects. For the individual trials, the SAE rate was 1.3% in the DRSP/EE group and 0.5% in the placebo group of Study 304049, and 0% during DRSP/EE exposure and 2.0% during placebo exposure in Study 305141.

Table 8 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
Miscarriage (231002)	Placebo	Unrelated	59 days after starting placebo	Severe	Recovered

Source: Table 91, a21566.pdf, Section 16, p 219 and Table 90, a07545.pdf, Section 14, p 306

Medical Reviewer's Comment:

- *In this reviewer's opinion, no SAEs were plausibly associated with DRSP/EE.*

7.1.3 Dropouts and Other Significant Adverse Events

The proportions of subjects who withdrew prior to completion of the two studies are shown in Table 9. Overall, the proportion withdrawing for any reason was higher in the DRSP/EE group (30.5%) as compared to the placebo subjects (24.0%). For the DRSP/EE subjects, the most common reason for withdrawal was an adverse event; for subjects on placebo, it was withdrawal of consent.

Table 9 Withdrawals during Treatment Phase – Pooled Data

Patient Disposition	DRSP/EE N=285		Placebo N=267	
	N	%	N	%
Completed Tx	198	69.5	203	76.0
Withdrew from Tx	87	30.5	64	24.0
Reason for Withdrawal				
Adverse event	40	14.0	11*	4.1
Lost to follow-up	20	7.0	18	6.7
Withdrawal of consent	16	5.6	21	7.9
Protocol deviation	5	1.8	10	3.7
Other	4	1.4	2	0.7
Pregnancy	1	0.4	1	0.4
Lack of efficacy	1	0.4	0	0

*One subject in Study 305141 was listed as withdrawn due to an adverse effect during placebo treatment; however, in actuality, she experienced a torn muscle in her back as a result of an accidental injury, and discontinued her medication (placebo) for approximately six weeks; she resumed the medication and completed TP1. She was then found to be pregnant during washout and was discontinued per protocol at that point.

Source: Text Table 4, iss.pdf, p 23

Medical Reviewer's Comment:

- *The difference in withdrawal rate between the DRSP/EE subjects and the placebo subjects was almost entirely due to withdrawals due to adverse events, which was more than three-*

fold higher in the DRSP/EE exposed subjects than in the placebo subjects (see section 7.1.3.2).

- **Withdrawal of consent, not further specified, occurred slightly more often in the placebo group.**

7.1.3.1 Overall profile of dropouts

The proportion of subjects who discontinued prematurely in each treatment arm is discussed in Section 7.1.3. Further discussion of dropouts in terms of baseline characteristics or efficacy results was not provided in the study reports.

Medical Reviewer's Comment:

- **At the FDA's request, the Applicant compiled tables of baseline and demographic characteristics of subjects who met the Full Analysis definition and who were and were not included in the mITT analysis (the latter being subjects who lacked post-baseline luteal phase DRSPS scores). Demographic characteristics were similar in both studies over the mITT subjects and the subjects excluded from the mITT. In Study 304049, baseline DRSPS scores were similar in both populations for DRSP/EE subjects, but were higher among placebo subjects who did not have luteal phase measurements (84.4 vs. 78.1). In Study 305141, the baseline DRSPS scores were higher in subjects who did not provide luteal phase data (83.0 for DRSP/EE subjects and 76.9 for placebo subjects, as compared to 71.3 for DRSP/EE subjects and 69.8 for placebo subjects who were included in the mITT population). This may suggest that subjects with more severe symptoms at entry were more likely to withdraw prematurely, particularly if assigned to placebo treatment initially.**

7.1.3.2 Adverse events associated with dropouts

Forty subjects terminated prematurely across the two clinical trials because of one or more adverse events that occurred during DRSP/EE exposure (14.0 %), as did 11 subjects during their exposure to placebo (4.1%). For the individual trials, the rate of withdrawal due to adverse events was 15.5% in the DRSP/EE group and 4.1% in the placebo group of Study 304049, and 7.4% during DRSP/EE exposure and 4.1% during placebo exposure in Study 305141. All adverse events leading to withdrawals are listed in Table 10.

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.**

Table 10 Treatment Withdrawals due to Adverse Events – Pooled Data

Preferred Term	DRSP/EE N=285		Placebo N=267	
	N	%	N	%
Nausea	13	4.6	3	1.1
Intermenstrual bleeding	8	2.8	0	0
Asthenia	7	2.5	1	0.4
Breast pain/tenderness	5	1.7	0	0
Depression	4	1.4	0	0
Nervousness	4	1.4	2	0.7
Headache	3	1.1	2	0.7
Emotional lability	3	1.1	0	0
Increased appetite	3	1.1	0	0
Menorrhagia	3	1.1	0	0
Vomiting	3	1.1	0	0
Abdomen enlarged	2	0.7	1	0.4
Acne	2	0.7	1	0.4
Breast engorgement	2	0.7	0	0
Constipation	2	0.7	0	0
Dysmenorrhea	2	0.7	0	0
Incoordination	2	0.7	0	0
Insomnia	2	0.7	0	0
Menstrual disorder	2	0.7	0	0
Palpitation	2	0.7	0	0
Spotting	2	0.7	0	0
Weight gain	2	0.7	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
Elevated potassium level**	1	0.4	0	0
Hot flashes	1	0.4	0	0
Hyperlipemia	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
Migraine	1	0.4	1	0.4
Sweating increased	1	0.4	1	0.4
Thrombocytopenia	1	0.4	0	0
Anxiety	0	0	2	0.7
Apathy	0	0	1	0.4
Chills	0	0	1	0.4
Eye pain	0	0	1	0.4
Hypertension	0	0	1	0.4
Pregnancy	0	0	1	0.4
Skin disorder	0	0	1	0.4

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

**This subject was actually withdrawn at the Applicant's request, and was not classified as withdrawn due to an adverse event in the Applicant's table

#Doppler showed no evidence of 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 and Table 91, Section 14, a07545.pdf, p 307

7.1.3.3 Other significant adverse events

7.1.3.3.1 Cardiovascular events

Due to the antimineralocorticoid actions of DRSP, there has been concern about hyperkalemia and associated cardiovascular adverse events resulting from use of drug products containing DRSP. Events that might be associated with hyperkalemia were reviewed by cardiologist consultants and included arrhythmias, palpitations, bradycardia, tachycardia, dizziness and syncope.

There were no cases of bradycardia or tachycardia in either study. Occurrence of the remaining selected cardiovascular adverse events is displayed in Table 11. None of the 12 subjects who experienced selected cardiovascular adverse events had an elevated potassium level at any point in the study.

Table 11 Selected Cardiovascular Adverse Events by Treatment – Pooled Data

Preferred Term	YAZ (24 days) (N=285) n (%)	Placebo (N=267) n (%)	Total (N=513) n (%)
Arrhythmia	1 (0.4)	0	1 (0.2)
Bradycardia	0	0	0
Dizziness	5 (1.8)	3 (1.1)	8 (1.6)
Palpitation	2 (0.7)	0	2 (0.4)
Syncope	0	1 (0.4)	1 (0.2)
Tachycardia	0	0	0
Total	8 (2.8)	4 (1.5)	12 (2.3)

AE = adverse event; N = total number of subjects treated; n = number of subjects with selected cardiovascular AEs.
 Note: Subjects are counted only once in a treatment group per cardiovascular AE in cases of multiple occurrence of the event.

Source: Text Table 15, iss.pdf, p 45

The 12 cases are discussed further, along with associated K⁺ levels:

- Subject #80036 (Study 305141, placebo→DRSP/EE) had **intermittent dizzy spells** during TP1; she was lost to follow-up in TP2. Run-in – 4.2, TP1/Cycle 2 – 4.6, unscheduled visit – 4.8, washout – 4.5 mEq/L
- Subject #270011 (Study 304049, placebo) experienced **moderate dizziness** for one day in Cycle 3. Run-in – 4.2, cycle 2 – 4.7, EOT – 4.2 mEq/L
- Subject #470079 (Study 304049, placebo) had two episodes of **mild dizziness** early in Cycle 1, each resolving after three days. Run-in – 3.9, cycle 2 – 3.6, EOT – 4.5 mEq/L
- Subject #520030 (Study 304049, placebo): experienced **syncope** at the end of study blood draw. Run-in – 4.1, EOT – 4.6 mEq/L
- Subject #120009 (Study 305141, DRSP/EE→placebo) experienced **dizziness** and had a **single near-syncope episode** on the first day she took DRSP/EE. She recovered and completed TP1, but withdrew consent during TP2. Run-in 4.2, TP1/Cycle 2 – 3.9, washout – 4.2, unscheduled visit 4.6, EOT 3.9 mEq/L

- Subject #30044 (Study 304049, DRSP/EE) experienced **severe dizziness** during a sinus infection for which she took a decongestant. Run-in – 4.9, cycle 2 – 4.5, EOT – 5.3 mEq/L
- Subject #180056 (Study 304049, DRSP/EE) had two weeks of **slight lightheadedness**, which resolved when she began taking the study drug at night. Run-in – 3.9, cycle 2 – 4.0, EOT – 3.6 mEq/L
- Subject #260001 (Study 304049, DRSP/EE) experienced breast tenderness, fatigue, **palpitations** and menstrual cramps leading to premature withdrawal from the study on Day 6. Run-in – 3.6, EOT – 4.0 mEq/L
- Subject #270010 (Study 304049, DRSP/EE) reported **mild occasional extra beats** at the EOT visit. Run-in – 4.1, cycle 2 – 4.0, EOT – 4.3 mEq/L
- Subject #500091 (Study 304049, DRSP/EE) had a cardiac history significant for mitral and tricuspid valve prolapse; she reported being **dizzy**, disoriented and shaky for two days beginning the day after randomization. This recurred for a single day five days later. Run-in – 4.4, cycle 2 – 4.4, EOT – 4.4 mEq/L
- Subject #840002 (Study 304049, DRSP/EE) had a mild episode of **palpitations** on Day 8. She was prematurely discontinued due to adverse events midway through second treatment cycle. Run-in – 3.9, EOT – 4.5 mEq/L
- Subject #840066 (Study 304049, DRSP/EE) had an episode of **mild lightheadedness** in Cycle 2, which resolved the next day. Run-in – 4.4, cycle 2 – 4.2, EOT – 4.9 mEq/L

Medical Reviewer's Comment:

- *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.*

7.1.3.3.2 Venous thromboembolic events

There were no venous thromboembolic events in either study.

Medical Reviewer's Comment:

- *In Study 304049, 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. In Study 305141, two subjects experienced the adverse event "pain in extremity" during exposure to DRSP/EE. One subject (#160001) experienced pain following knee surgery during the DRSP/EE treatment period. The second subject (#80037) reported intermittent bilateral leg pain and numbness over a two-month period while on DRSP/EE; no evaluation appears to have been done, but this is unlikely to represent a thromboembolic event.*

7.1.3.3.3 Pregnancies

A total of five pregnancies occurred in the two clinical trials (see Table 12).

Medical Reviewer's Comment:

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

Table 12 List of Pregnancies in Studies 304049 & 305141

Study	Subject #	Drug Treatment	Timing of conception	Pregnancy outcome
304049	160021	DRSP/EE	3 weeks following last dose	Healthy child
304049	30017	Placebo	Pregnancy diagnosed at EOT visit, 3 days after last dose	Healthy child
305141	230012	DRSP/EE→placebo	During placebo treatment	Miscarriage (SAE)
305141	200014	DRSP/EE→placebo	Pregnancy diagnosed during washout, 33 days after last dose of DRSP/EE and one month after LMP	Lost to follow-up
305141	80004	Placebo→DRSP/EE	Pregnancy diagnosed during washout, 45 days after last dose of placebo and five weeks after LMP	Elective abortion

7.1.4 Other Search Strategies

No signals of toxicity requiring additional investigation were noted.

7.1.5 Common Adverse Events

A total of 79% of DRSP/EE subjects experienced at least one adverse event considered to be treatment emergent, as opposed to 64% of subjects during placebo exposure. Table 13 shows the adverse events occurring with $\geq 2\%$ incidence in the two pivotal trials.

Events that occurred with at least twice the frequency in DRSP/EE vs. placebo subjects were:

- Intermenstrual bleeding
- Nausea
- Breast pain
- Libido decreased
- Emotional lability
- Nervousness
- Pain in extremity (see comment in Section 7.1.3.3.2)
- Depression
- Migraine
- Hyperlipemia
- Increased appetite

Table 13 Most Common Adverse Events (≥ 2%) – Pooled Data

Preferred Term	DRSP/EE N=285		Placebo N=267	
	N	%	N	%
Intermenstrual bleeding	69	24.2	11	4.1
Headache	53	18.6	51	19.1
Nausea	53	18.6	16	6.0
Breast pain	37	13.0	13	4.9
Upper respiratory infection	32	11.2	27	10.1
Asthenia	23	8.1	12	4.5
Abdominal pain	13	4.6	8	3.0
Libido decreased	13	4.6	3	1.1
Emotional lability	11	3.9	5	1.9
Suspicious Pap smear	11	3.9	7	2.6
Menorrhagia	10	3.5	4	1.5
Nervousness	10	3.5	4	1.5
Pain in extremity	10	3.5	1	0.4
Depression	9	3.2	2	0.7
Menstrual disorder	9	3.2	5	1.9
Migraine	9	3.2	4	1.5
Sinusitis	9	3.2	14	5.2
Weight gain	9	3.2	8	3.0
Vaginal moniliasis	8	2.8	7	2.6
Vaginitis	8	2.8	8	3.0
Hyperlipemia	7	2.5	1	0.4
Back pain	7	2.5	4	1.5
Diarrhea	7	2.5	5	1.9
Increased appetite	7	2.5	0	0
Abdomen enlarged	6	2.1	6	2.2
Accidental injury	6	2.1	9	3.4
Acne	6	2.1	7	2.6
Dysmenorrhea	6	2.1	10	3.7
Urinary tract infection	5	1.8	9	3.4
Flu syndrome	2	0.7	6	2.2
Tooth disorder	2	0.7	6	2.2
Bronchitis	1	0.4	6	2.2

Number of individual events exceeds total, because some subjects experienced multiple events

Source: Text Table 11, iss.pdf, pp 35-7

Medical Reviewer's Comment:

- **Most of the adverse events occurring more frequently with DRSP/EE fall into three clusters (mood, breast and menstrual disorders), which represent adverse events commonly reported with oral contraceptives and discussed in the labeling for Yasmin. Migraines, nausea, hypertriglyceridemia and changes in libido are also commonly associated with oral contraceptive use. The do not suggest a safety profile of greater concern than any other oral contraceptive. The preponderance of these events in the DRSP/EE group does not suggest a safety profile of greater concern than any other oral contraceptive.**

7.1.5.1 Eliciting adverse events data in the development program

In both trials, in addition to spontaneous reports, adverse events were elicited at each visit by general questions about any health problems beyond usual PMDD symptoms. Adverse events were defined as any untoward medical occurrence in a patient receiving study drug, regardless of potential causality. In all discussions of adverse events occurring in Study 305141, the adverse event was attributed to the drug which the subject was taking at the time of onset of the event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events that began prior to treatment but had maximum intensities of moderate, severe or unknown were categorized as treatment-emergent events in Study 304049.

Adverse events were coded according to the Hoechst 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).***

7.1.5.3 Incidence of common adverse events

See Section 7.1.5.

7.1.5.4 Common adverse event tables

See Table 13.

7.1.5.5 Identifying common and drug-related adverse events

The proportion of adverse events considered by the investigators to be drug-related was greater in the DRSP/EE treatment group as compared to the placebo group. Events categorized by the Applicant as possibly, probably or definitely drug-related are presented in Table 14.

Medical Reviewer's Comments:

- ***Events of intermenstrual bleeding, nausea, breast pain, decreased libido, emotional lability, menorrhagia and migraine all occurred with at least twice the frequency in the subjects exposed to DRSP/EE as compared to placebo. As noted previously, most of these events are known to be associated with oral contraceptive use, and are labeled in the Yasmin label.***

Table 14 Most Common Drug-Related Adverse Events (≥ 2%) – Pooled Data

Preferred Term	DRSP/EE N=285		Placebo N=267	
	N	%	N	%
Intermenstrual bleeding	65	22.8	10	3.7
Headache	38	13.3	26	9.7
Nausea	48	16.8	12	4.5
Breast pain	31	10.9	10	3.7
Asthenia	14	4.9	7	2.6
Abdominal pain	6	2.1	3	1.1
Libido decreased	13	4.6	3	1.1
Emotional lability	10	3.5	3	1.1
Menorrhagia	10	3.5	3	1.1
Menstrual disorder	9	3.2	5	1.9
Nervousness	8	2.8	4	1.5
Depression	8	2.8	0	0
Migraine	4	1.4	1	0.4
Weight gain	7	2.5	5	1.9
Abdomen enlarged	5	1.8	6	2.2

Number of individual events exceeds total, because some subjects experienced multiple events
 Source: Text Table 14, ise.pdf, pp 42-4

7.1.5.6 Additional analyses and explorations

No safety signals of sufficient concern to warrant further investigation were noted.

7.1.6 Less Common Adverse Events

No additional adverse event signals of concern were noted.

7.1.7 Laboratory Findings

Chemistry

The major focus of the analysis of chemistry laboratory values was to assess the potential effect of DRSP/EE, as an antimineralocorticoid, on potassium concentrations. The number of subjects with potassium levels > 5.4 mEq/L is shown in Table 15. The proportions in each treatment group were similar (1.4% of DRSP/EE subjects, 1.1% of placebo subjects). None of these subjects experienced any of the cardiovascular adverse events potentially associated with hyperkalemia, and only one subject in each treatment arm was taking a concomitant medication (NSAID) thought to affect potassium levels. All except two of the placebo subjects normalized their values while remaining on treatment. Only one elevated value (subject #380112 in Study 304049, assigned to DRSP/EE, who increased from a baseline level of 4.4 mEq/L to 6.0 at Cycle 2, and then returned to normal by the end of treatment) was considered by the investigator to be clinically relevant.

Table 15 Subjects with Elevated Post-treatment Potassium Values – Pooled Data

Report Number	Treatment	Subject	Visit	Postbaseline Serum Potassium	Serum Creatinine	Creatinine Clearance	Creatinine Clearance
				≥5.5 mEq/L	(mg/dL)	(mL/min)	Category*
A21566	YAZ	200056	Treatment Cycle 2 (31 days)	5.5	1.0	69.1	mild
	YAZ	380122	Treatment Cycle 2 (26 days)	6.0	0.9	81.6	normal
	YAZ	510008	Treatment Cycle 2 (30 days)	5.7	0.6	129.9	normal
	Placebo	840058	End of Treatment Cycle (127 days)	5.6	0.6	145.2	normal
A07545	YAZ	80001	End of Treatment Cycle (87 days)	5.6	1.0	67.2	mild
	Placebo	80021	Treatment Cycle 2 (140 days)	5.7	0.7	116.0	normal
	Placebo	80039	End of Treatment Cycle (246 days)	6.2	4.2	27.6	severe

*Creatinine clearance categories: >80 mL/min = normal; 50 to ≤80 mL/min = mild; 30 to ≤50 mL/min = moderate; ≤30 mL/min = severe.

Source: Text Table 21, iss.pdf, p 61

Change from baseline in potassium level was minimal, and similar between treatment arms, as shown in Table 16.

Table 16 Change from Baseline in Potassium Level – Pooled Data

Treatment	Number of Subjects ^a	Baseline Mean ± SD	Change from Baseline in	
			Postbaseline Maximum ^b Mean ± SD	Postbaseline Average ^b Mean ± SD
YAZ	255	4.27 ± 0.374	0.17 ± 0.431	0.04 ± 0.394
Placebo	245	4.23 ± 0.359	0.18 ± 0.393	0.04 ± 0.360

SD = standard deviation.
 Note: Normal ranges of serum potassium are 3.4 – 5.4 mEq/L for Report A21566 and 3.6 – 5.2 mEq/L for Report A07545.
^aNumber of subjects who had a baseline and at least 1 postbaseline serum potassium value.
^bAll serum potassium values, including results from unscheduled and repeat visits, were used in the calculation of average and maximum serum potassium values.

Source: Text Table 22, iss.pdf, p 65

The percent of subjects with transitions in potassium values from normal findings at baseline to values outside the normal range over all treatment visits was greater in the DRSP/EE group (2.8%) than the placebo group (1.6%) (see Table 17).

Table 17 Transitions* in Potassium Values with Treatment – Pooled Data

Parameter	Treatment Cycle	Treatment Group	Baseline Value (%)	Low (%)	Normal (%)	High (%)	Total (%)	
Potassium	All	DRSP/EE	Low (%)	0	1 (0.4)	0	1 (0.4)	
			Normal (%)	1 (0.4)	245 (96.1)	7 (2.8)	253 (99.2)	
			High (%)	0	1 (0.4)	0	1 (0.4)	
			Total (%)	1 (0.4)	247 (96.9)	7 (2.8)	255 (100)	
			Placebo	Low (%)	0	2 (0.8)	0	2 (0.8)
				Normal (%)	2 (0.8)	237 (96.7)	4 (1.6)	243 (99.2)
				High (%)	0	0	0	0
				Total (%)	2 (0.8)	239 (97.6)	4 (1.6)	245 (100)

* Normal range varied slightly over the two studies, with an upper limit of normal of 5.4 mEq/L in Study 304049 and of 5.2 mEq/L in Study 305141

Source: Table 38, ise.pdf, pp 472

Medical Reviewer's Comment:

- **A small but increased percent of DRSP/EE subjects as compared to placebo subjects had increases in potassium level 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.**

In addition, creatinine clearance, calculated using the standard formula for females, was assessed as a measure of renal function that may affect potassium balance (see Table 18). In the DRSP/EE group, 2.3% of subjects experienced a shift from normal function to mild renal impairment, compared to 3.3% of placebo subjects.

Table 18 Transitions in Creatinine Clearance with Treatment – Pooled Data

Parameter	Treatment Cycle	Treatment Group (N)	Baseline Value (%)	Normal (%)	Mild (%)	Moderate (%)	Severe (%)
Creatinine Clearance	EOT	DRSP/EE (256)	Normal (%)	243 (94.9)	6 (2.3)	0	0
			Mild (%)	6 (2.3)	1 (0.4)	0	0
			Moderate (%)	0	0	0	0
			Severe (%)	0	0	0	0
		Placebo (242)	Normal (%)	226 (93.4)	8 (3.3)	0	1* (0.4)
			Mild (%)	3 (1.2)	4 (1.7)	0	0
			Moderate (%)	0	0	0	0
			Severe (%)	0	0	0	0

* This subject, #80039 in the placebo group, had elevations in creatinine clearance, creatinine and potassium that were determined to be spurious
 Source: Table 41, ise.pdf, pp 481

Medical Reviewer's Comment:

- **There does not appear to be an increased risk of renal impairment with DRSP/EE use.**

The percent of subjects with transitions in lipid values from normal findings at baseline to values outside the normal range over treatment was greater than for any other chemistry parameter (see Table 19). Triglyceride levels were most affected by treatment, with 14.1% of DRSP/EE subjects and 6.6% of placebo subjects with normal baseline values experiencing increased levels. For cholesterol, 9.8% of DRSP/EE subjects with normal baseline values experienced increased levels, as compared to 4.5% of placebo subjects, while for LDL, 6.7% of DRSP/EE subjects with normal baseline values experienced increased levels, as compared to 3.7% of placebo subjects. For HDL (not shown), 0.4% of DRSP/EE subjects and 1.2% of placebo subjects with normal baseline levels developed low levels.

The mean change from baseline was statistically significantly different between DRSP/EE and placebo groups for total cholesterol and triglycerides. The mean change in cholesterol from baseline to EOT for DRSP/EE subjects was 14.9 mg/dl, compared to -3.7 for placebo users. For triglycerides, the mean change from baseline to EOT for DRSP/EE subjects was 27.2 mg/dl, compared to -0.2 for placebo users. In all cases, however, mean values for lipids remained within the normal range.

Table 19 Transitions in Lipid Values with Treatment – Pooled Data

Parameter	Treatment Cycle	Treatment Group	Baseline Value (%)	Low (%)	Normal (%)	High (%)	Total (%)
Total Cholesterol	EOT	DRSP/EE	Low (%)	1 (0.4)	10 (3.9)	0	11 (4.3)
			Normal (%)	3 (1.2)	183 (71.5)	25 (9.8)	211 (82.5)
			High (%)	0	6 (2.3)	28 (10.9)	24 (13.2)
			Total (%)	4 (1.6)	199 (77.8)	53 (20.5)	246 (100)
		Placebo	Low (%)	8 (3.3)	3 (1.2)	0	9 (4.5)
			Normal (%)	12 (4.9)	184 (75.4)	11 (4.5)	190 (84.8)
			High (%)	0	12 (4.9)	14 (5.7)	24 (10.7)
			Total (%)	20 (8.2)	199 (81.6)	25 (10.2)	222 (100)
Triglycerides	EOT	DRSP/EE	Low (%)	2 (0.8)	6 (2.4)	0	8 (3.2)
			Normal (%)	0	170 (66.7)	36 (14.1)	206 (80.8)
			High (%)	0	11 (4.3)	30 (11.8)	41 (16.1)
			Total (%)	2 (0.8)	187 (77.3)	66 (25.9)	254 (100)
		Placebo	Low (%)	2 (0.8)	3 (1.2)	0	5 (2.0)
			Normal (%)	1 (0.4)	198 (81.5)	16 (6.6)	215 (88.5)
			High (%)	0	10 (4.1)	13 (5.4)	23 (9.5)
			Total (%)	3 (1.2)	211 (86.8)	29 (11.9)	243 (100)
LDL	EOT	DRSP/EE	Low (%)	10 (3.9)	11 (4.3)	0	21 (8.3)
			Normal (%)	4 (1.6)	186 (73.2)	17 (6.7)	207 (81.5)
			High (%)	0	3 (1.2)	23 (9.1)	26 (10.2)
			Total (%)	14 (5.5)	200 (78.7)	40 (15.8)	254 (100)
		Placebo	Low (%)	11 (4.5)	4 (1.7)	0	15 (6.2)
			Normal (%)	13 (5.4)	183 (75.3)	9 (3.7)	205 (84.4)
			High (%)	0	2 (0.8)	21 (8.6)	23 (9.4)
			Total (%)	24 (9.9)	189 (77.8)	30 (12.4)	243 (100)

Source: Table 47, ise.pdf, pp 517-8, 527-8, 535-6

Medical Reviewer's Comment:

- **As is recognized for oral contraceptives generally, DRSP/EE had an adverse impact on lipids, primarily affecting triglycerides and total cholesterol.**

For all other chemistry parameters, fewer than 4% of subjects in either treatment arm had transitions from normal findings at baseline to values outside the normal range over treatment.

Hematology

Fewer than 5% of subjects in either treatment arm had transitions from normal findings at baseline to values outside the normal range over treatment.

Urinalysis

Fewer than 6% of subjects had transitions from normal findings at baseline to values outside the normal range over treatment, and only on Specific Gravity was the proportion greater in the DRSP/EE than the placebo subjects. On this measure, 9.7% of DRSP/EE subjects shifted from normal to low, compared to 4% of placebo subjects.

Medical Reviewer's Comment:

- **The higher percent of DRSP/EE vs. placebo subjects shifting to low Specific Gravity may reflect the diuretic properties of DRSP. It is not believed to be of clinical significance.**

7.1.7.1 Overview of laboratory testing in the development program

See Section 7.1.7.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory data were reviewed for the two pivotal, placebo-controlled studies for the PMDD indication.

7.1.7.3 Standard analyses and explorations of laboratory data

See Section 7.1.7.

7.1.7.4 Additional analyses and explorations

In addition to laboratory assessments, the Applicant evaluated subjects for the effect of use of NSAIDs, aspirin or other products containing drugs that might cause hyperkalemia. Only one subject in each treatment group who experienced potassium levels > 5.4 mEq/L was taking a relevant concomitant medication (NSAIDs in both cases).

The impact of renal impairment on potassium concentrations was also assessed, since the effect of DRSP is on renal tubular management of potassium. The renal function of subjects experiencing elevated potassium levels during treatment is shown in Table 15. The change in potassium level stratified by baseline renal function is displayed in Table 20.

Table 20 Change in Potassium by Renal Function – Pooled Data

Baseline Creatinine Clearance Category*	Statistics	YAZ (24 days)			Placebo		
		Baseline Serum K ⁺ Value	Maximum Serum K ⁺ Value	Change from Baseline to Maximum Value	Baseline Serum K ⁺ Value	Maximum Serum K ⁺ Value	Change from Baseline to Maximum Value
Normal ^b	n	250	248	248	236	236	236
	Mean ± SD	4.28 ± 0.373	4.44 ± 0.412	0.16 ± 0.426	4.23 ± 0.356	4.42 ± 0.398	0.19 ± 0.391
	Median	4.20	4.40	0.20	4.20	4.30	0.20
	Min -Max	3.4 - 5.6	3.6 - 6.0	-1.3 - 1.6	3.2 - 5.4	3.7 - 6.2	-0.7 - 1.8
Mild ^c	n	8	7	7	7	7	7
	Mean ± SD	4.15 ± 0.378	4.37 ± 0.613	0.31 ± 0.604	4.27 ± 0.454	4.21 ± .308	-0.06 ± 0.493
	Median	4.20	4.20	0.40	4.20	4.30	0.10
	Min -Max	3.6 - 4.8	3.7 - 5.6	-0.5 - 1.4	3.7 - 5.1	3.6 - 4.5	-0.6 - 0.8

Source: Text Table 24, ise.pdf, p 69

Medical Reviewer's Comment:

- *It appears that subjects with mild renal impairment at baseline who take DRSP/EE do experience greater mean change in potassium than do placebo subjects, or subjects with normal renal function. The proposed labeling contraindicates DRSP/EE for subjects with moderate to severe renal insufficiency.*

Assessment of cardiovascular events potentially associated with hyperkalemia is discussed in Section 7.1.3.3. The association of cardiovascular events with renal function was also evaluated. Among the eleven subjects on DRSP/EE who had mild renal impairment, one reported dizziness and one reported palpitations. None of the seven placebo subjects with mild renal impairment had any cardiovascular events.

7.1.7.5 Special assessments

No additional special laboratory assessments were conducted.

7.1.8 Vital Signs

Blood pressure and pulse were assessed at each study visit. Mean values for blood pressure and pulse, by drug treatment, at each treatment cycle are presented in Table 21.

Table 21 Mean (SD) Blood Pressure and Pulse by Treatment Period and Drug Exposure

Vital Sign	Treatment	Run-in 1	Run-in 1	Cycle 1	Cycle 2	Cycle 3	EOT
Systolic BP (mm Hg)	N	229	231	285	229	201	261
	DRSP/EE	110.9 (10.5)	109.7 (10.6)	111.3 (11.9)	110.1 (11.1)	111.5 (11.0)	110.0 (11.4)
	N	216	216	266	228	208	252
	Placebo	109.7 (10.5)	109.0 (10.4)	111.3 (10.6)	110.2(10.5)	110.8 (11.4)	110.0 (11.9)
Diastolic BP (mm Hg)	N	229	231	285	229	201	261
	DRSP/EE	71.0 (8.5)	71.3 (8.3)	71.1 (8.5)	71.4 (8.4)	71.9 (8.5)	71.7 (9.1)
	N	216	216	266	227	208	252
	Placebo	70.1 (7.8)	70.1 (7.8)	71.2 (8.4)	71.1 (7.8)	70.6 (8.6)	70.7 (8.1)
Pulse (BPM)	N	230	229	285	229	201	261
	DRSP/EE	71.1 (9.8)	70.1 (9.3)	71.2 (8.8)	70.3 (8.7.)	72.0 (9.7)	72.6 (9.7)
	N	215	218	266	228	207	252
	Placebo	70.2 (9.2)	70.1 (8.3)	70.4 (9.0)	69.9 (9.7)	71.3 (9.1)	70.3 (9.1)

Source: Table 53, iss.pdf, p 613-22

In Study 304049, 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 slightly higher values for pulse and diastolic blood pressure at the end of treatment in the DRSP/EE subjects are consistent with the higher baseline values and are not believed to be clinically significant.*

7.1.8.1 Overview of vital signs testing in the development program

Only systolic and diastolic blood pressure and pulse were assessed in Study 305141. Study 304049 also evaluated temperature.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs data were reviewed for the two pivotal, placebo-controlled studies for the PMDD indication.

7.1.8.3 Standard analyses and explorations of vital signs data

See Section 7.1.8.

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations were conducted.

7.1.9 Electrocardiograms (ECGs)

Electrocardiographic monitoring was not performed in these trials. DRSP/EE has been to reproductive aged women for contraception since 2001 with no evidence of effect on ECG parameters.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG monitoring was not performed in these trials.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

ECG monitoring was not performed in these trials.

7.1.9.3 Standard analyses and explorations of ECG data

ECG monitoring was not performed in these trials.

7.1.9.4 Additional analyses and explorations

ECG monitoring was not performed in these trials.

7.1.10 Immunogenicity

Data on potential Immunogenicity was not submitted by the Applicant.

7.1.11 Human Carcinogenicity

Data on potential human carcinogenicity was not submitted by the Applicant. The standard oral contraceptive labeling statements concerning epidemiological studies that attempt to assess the risk of cancer of the reproductive organs and breast associated with oral contraceptive use is included in the proposed label.

7.1.12 Special Safety Studies

No special safety studies were conducted. Issues of specific concern relating to potential actions of DRSP/EE were monitored, as discussed in Section 7.1.3.3.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal effects were noted in any subject upon discontinuation of DRSP/EE. No abuse potential for this drug is expected.

7.1.14 Human Reproduction and Pregnancy Data

The drug is indicated for prevention of pregnancy. Yasmin is a pregnancy Category X drug, and the proposed label lists known or suspected pregnancy as a contraindication to use. Fourteen pregnancies are known to have occurred with *in utero* Yasmin exposure; one infant was born with esophageal atresia. It is unknown if this is a causal association. Eleven pregnancies with YAZ exposure in utero have been identified, with no known congenital anomalies occurring.

7.1.15 Assessment of Effect on Growth

Oral contraceptives generally have been shown to decrease the quantity of breast milk, and small amounts of contraceptive steroids are excreted in breast milk. A few adverse effects on nursing children, such as jaundice and breast enlargement, are noted in the proposed label. The proposed label recommends use of other contraceptive methods until weaning.

7.1.16 Overdose Experience

No cases of overdose (defined as ingestion of ≥ 3 doses in a day) occurred in the two clinical trials. Tolerability studies are noted by the Applicant to demonstrate good tolerability of DRSP doses from 10-100 mg. However, due to the antiminerlocorticoid properties of DRSP, serum concentrations of potassium and sodium, and evidence of metabolic acidosis, should be monitored in case of overdose.

7.1.17 Postmarketing Experience

Postmarketing data related to Yasmin are discussed in the review of NDA 21-676. YAZ is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The studies providing safety data were the two phase 3 randomized, placebo-controlled, double-blind clinical trials for the PMDD indication, which were conducted in the U.S. In Studies 304049 and 305141, a total of 285 subjects were exposed to DRSP/EE, with 194 of these receiving the planned 3 cycles of treatment. The total of 513 subjects receiving DRSP/EE (N=285) and/or placebo (N=267) comprised the safety population (numbers total >513 due to cross-over study where subjects were exposed to both DRSP/EE and placebo).

7.2.1.2 Demographics

Pooled data from Studies 304049 and 305141 provided the demographic information displayed in Table 22. Overall, the two groups are similar.

Medical Reviewer's Comments:

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

**APPEARS THIS WAY
ON ORIGINAL**