Medical Reviewer's Comment:

- *The populations appear comparable at baseline.*

Table 49 Study 305141: Demographic Characteristics of ITT Population

| Variable	Statistics/Class	Treatment Assignment		Total
		DRSP/EE→Placebo N = 34	Placebo→ DRSP/EE N = 30	
Age (years)	n	34	30	64
	Mean ±SD	31.9 ±4.74	31.8 ±6.38	31.8 ±5.52
	Median	31.0	33.0	32.0
	Minimum-Maximum	19 - 39	20 - 40	19 – 40
Ethnic group	Caucasian	23 (67.65%)	25 (83.33%)	48 (75.00%)
(n [%])	Black	4 (11.76%)	3 (10.00%)	7 (10.94%)
	Hispanic	3 (8.82%)	2 (6.67%)	5 (7.81%)
	Asian	1 (2.94%)	0 (0.00%)	1 (1.56%)
	Other	3 (8.82%)	0 (0.00%)	3 (4.69%)
Weight (kg)	n	34	30	64
	Mean ±SD	68.64 ±16.394	73.33 ±13.458	70.84 ±15.157
	Median	65.55	73.94	68.04
	Minimum-Maximum	45.7 – 99.8	51.7 – 107.5	45.7 – 107.5
Height (cm)	n	34	30	64
	Mean ±SD	162.19 ±5.971	165.48 ±7.160	163.73 ±6.710
	Median	162.56	164.15	162.56
	Minimum-Maximum	149.9 – 172.7	144.8 – 180.3	144.8 – 180.3
BMI (kg/m 2)	n	34	30	64
	Mean ±SD	26.064 ±5.477	26.670 ±4.784	26.348 ±5.132
	Median	25.000	24.900	25.000
	Minimum-Maximum	17.20 – 35.50 a	20.00 – 34.00	17.20 – 35.50

Source: Text Table 6, a07545.pdf, p 70

Baseline scores on the first 21 items of the DRSPS are discussed in Section 10.2.8.1. There were no significant differences between the scores in the two treatment arms the treatment arms at the first baseline visit. Comparability of scores in the two treatment arms following the wash-out cycle is also discussed in Section 10.2.8.1.

10.2.7.2 Withdrawals, compliance, and protocol violations

A total of 20 of 34 DRSP/EE→placebo (58.8%) and 19 of 30 placebo→DRSP/EE subjects (63.3%) discontinued the trial, as illustrated in Figure 5. Among subjects randomized to DRSP/EE→placebo, 24% of subjects withdrew during TP1, while taking DRSP/EE, and 26% of remaining subjects withdrew during TP2, while assigned to placebo. Among subjects randomized to placebo→DRSP/EE, 27% of subjects withdrew during TP1, while taking placebo, and 45% of remaining subjects withdrew during TP2, while receiving DRSP/EE. Overall, pooling treatment arms and omitting withdrawals during the wash-out period, 17 of 54 subjects (31.5%) withdrew prematurely while receiving DRSP/EE, while 13 of 49 subjects (26.5%) withdrew while receiving placebo.

Figure 5 Flow Chart of Subject Withdrawal
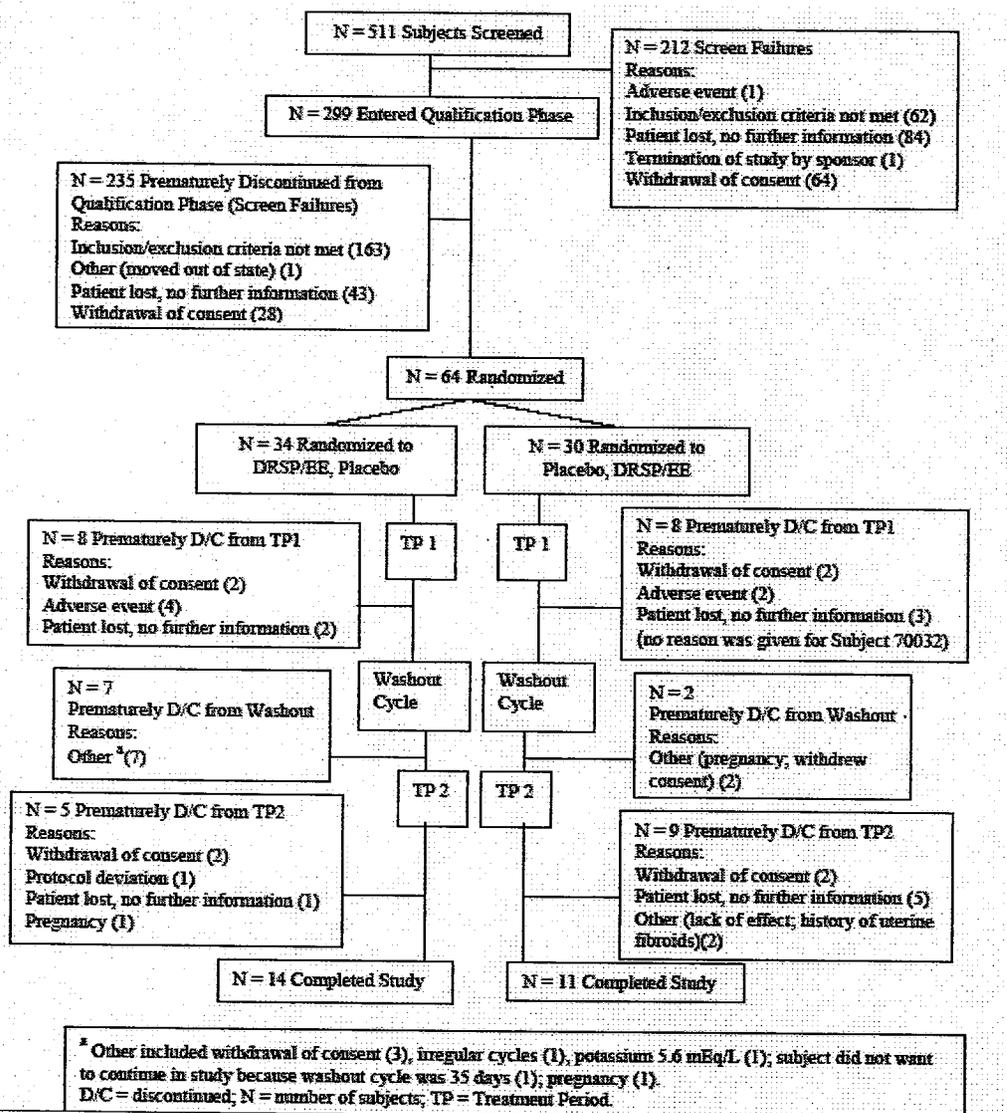
Source: Text Figure 1, a07545.pdf, p 65

Medical Reviewer's Comment:

- *The withdrawal rate is similar over treatment arms and treatment periods with the exception of an elevated rate among subjects assigned to DRSP/EE in TP2. More than 50% of these withdrawn subjects are listed as "lost to follow-up."*

Reasons for withdrawal are shown in Table 50. In total, six subjects withdrew due to adverse events during the trial, four while receiving DRSP/EE and two while on placebo.

Table 50 Study 305141: Detailed Reason for Withdrawal from Treatment

Patient Disposition	Study 305141			
	DRSP/EE→Placebo N=34		Placebo→DRSP/EE N=30	
	N	%	N	%
Completed Treatment	14	41.2	11	36.7
Withdrew from Treatment	20	58.8	19	63.3
Treatment Period 1	8	23.5	8	26.7
Wash-out Phase	7	20.6	2	6.7
Treatment Period 2	5	14.7	9	30.0
Reason for Withdrawal				
Protocol violation	1	2.9	1	3.3
Adverse event	4	11.8	2	6.7
Lack of efficacy	0	0	1	3.3
Consent withdrawn	7	20.6	5	16.7
Lost to follow-up	3	8.8	8	26.7
Pregnancy	2	5.9	1	3.3
Other*	3	8.8	1	3.3
Reason for Withdrawal by Drug Assignment at Withdrawal	DRSP/EE N=54		Placebo N=49	
Total withdrawn/**	17	31.5	13	26.5
Protocol violation	1	1.9	1	2.0
Adverse event	4	7.4	2	4.1
Lack of efficacy	1	1.9	0	0
Consent withdrawn	4	7.4	4	8.2
Lost to follow-up	7	13.0	4	8.2
Pregnancy	0	0	1	2.0
Other***	0	0	1	2.0

* includes: irregular cycles, K+ 5.6 mEq/L, length of washout period; no reason given
**Exclusive of subjects who withdrew during washout period
***includes: no reason given
Source: Based on Text Figure 1, a07545.pdf, p 65

Medical Reviewer's Comment:

- *At the FDA's request, the Applicant reviewed all comment fields in the database to determine the reasons behind withdrawal of consent; no further information was obtained.*
- *No additional information about the subjects lost to follow-up was provided.*
- *When viewed by drug assignment at time of withdrawal, withdrawal due to adverse event (4 vs. 2 subjects) and due to loss to follow-up (7 vs. 4) occurred almost twice as frequently in the DRSP/EE subjects as in subjects receiving placebo.*
- *At the FDA's request, the Applicant further broke out the reason for withdrawal by treatment period and drug assignment. Half of subjects who received DRSP/EE and withdrew in TP1 withdrew due to adverse events. Of those receiving DRSP/EE in TP2 who withdrew, none was attributed to an adverse event; over half were lost to follow-up. More than half of the DRSP/EE subjects who withdrew during washout did so by withdrawing consent. This may reflect the worsening of their symptoms during washout and their suspicion that they would then be embarking upon placebo treatment. Placebo subjects, at all phases of the study, terminated prematurely primarily due to consent withdrawal and loss to follow-up. Thus, it is difficult to know how to interpret withdrawals after TP1, as the majority are attributed to non-specific reasons.*

Compliance was based upon daily recording of tablet intake in subject diaries. If diary data were missing, recorded usage was supplemented by data based upon return of unused or partially used blister packs at

the clinical visits. A written explanation was required if there were an imbalance between recorded usage and the number used according to dispensed minus returned pills. Compliance with DRSP/EE was unable to be calculated for nine subjects and with placebo for five subjects. Mean compliance with DRSP/EE was 94.4% and with placebo 95.8%. Among all subjects, 42 (65.6%) were ≥ 75% compliant.

Protocol violations occurred in all 34 DRSP/EE→placebo subjects (100%) and in 27 placebo→DRSP/EE subjects (90%), with major deviations in 64.7% of the DRSP/EE→placebo group and in 66.7% of the placebo→DRSP/EE group. These 42 subjects with major protocol violations were excluded from the Per Protocol analysis. Major protocol violations included (numbers total >42 since some subjects had multiple violations):

- Deviations in entry criteria
  - 7 violations occurred in DRSP/EE→placebo subjects
  - 4 violations occurred in placebo→DRSP/EE subjects
- Treatment/procedure deviations (includes no DRSPS calculation in one or more treatment periods, <75% compliance, taking multiple pills on ≥ three days and lack of wash-out cycle [placebo→DRSP/EE subject])
  - 20 violations occurred in DRSP/EE→placebo subjects
  - 21 violations occurred in placebo→DRSP/EE subjects
- Use of excluded concomitant medication
  - 3 violations occurred in DRSP/EE→placebo
  - 2 violations occurred in placebo→DRSP/EE subjects
- Other (blood in urine during wash-out period)
  - 1 violation occurred in placebo→DRSP/EE subject

10.2.8　Efficacy

10.2.8.1 Key Efficacy Assessments

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

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

The primary efficacy analysis was done on the "full analysis" or modified ITT 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 violations of inclusion/exclusion criteria, had a major protocol violation or failed to provide a DRSPS score for at least one treatment cycle in each treatment period) was also used to analyze the primary efficacy variable.

10.2.8.2 Pharmacokinetic Assessments

Pharmacokinetic sampling was not done in this study.

10.2.8.3 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was the change from baseline in the average over three treatment cycles of the first 21 items of the DRSPS. For each cycle, the first 21 items were averaged over the five days preceding menses, and then summed. The primary efficacy variable was the difference between treatment arms in change in the average of the non-missing treatment cycle scores (from 1-3 scores averaged per subject) from the baseline score. The baseline score for TP1 was averaged over the two run-in cycles; for TP2, baseline scores were based on the single washout cycle.

Cycles were based on the first recording of menses in the diary; for subjects with any amenorrhea, where cycle stop/start dates could not be determined, determination of the dates when pills 20-24 were taken was made from manual review of the diary prior to unblinding. If an item was missing for a day during the five days preceding menses, the missing item was imputed by averaging the two non-missing bordering days' values. Thus, data missing from day 1 or 5 prior to menses could not be imputed due to lack of qualifying bordering days. If more than two days of an item were missing after the above imputation was done, the item average was set as missing. If the average of any of the 21 DRSPS items were missing, then the overall DRSPS score was set to missing as well.

Medical Reviewer's Comments:

- *DNDP had recommended that luteal phase DRSPS ratings be obtained over the full seven days of the late phase, and requested that the Applicant justify any decision to use less than the full seven day period. However, as noted in the Reviewer's Comment in Section 10.1.2, the reviewer does not believe that use of the shorter luteal phase period compromises the validity of the data.*

- *The Division had recommended that missing data be imputed by averaging all non-missing data points for that cycle; instead the Applicant has averaged only the two bordering days' data. However, 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.*

- *Table 51 displays the DRSPS scores by treatment sequence and cycle.*

Table 51 DRSPS Scores by Treatment Sequence and Cycle

Cycle		Treatment Sequence	
		DRSP/EE, Placebo N = 34	Placebo, DRSP/EE N = 30
Run-in cycle 1	n	34	29
	Mean ± SD	74.13 ± 17.771	72.48 ± 19.069
	Median	70.00	68.80
	Minimum – Maximum	49.2 – 117.8	36.4 – 111.8
Run-in cycle 2	n	33	29
	Mean ± SD	74.72 ± 22.023	70.08 ± 20.087
	Median	69.60	62.40
	Minimum – Maximum	39.6 – 123.0	44.0 – 113.4
Treatment cycle 1	n	26	23
	Mean ± SD	37.78 ± 13.823	50.12 ± 20.503
	Median	35.80	49.60
	Minimum – Maximum	21.2 – 76.4	21.0 – 86.0
Treatment cycle 2	n	26	20
	Mean ± SD	38.47 ± 18.978	50.09 ± 25.276
	Median	30.30	38.60
	Minimum – Maximum	21.0 – 95.7	21.0 – 108.2
Treatment cycle 3	n	25	18
	Mean ± SD	35.54 ± 12.707	52.33 ± 21.359
	Median	31.20	44.60
	Minimum – Maximum	21.0 – 65.6	24.6 – 95.6
Washout cycle	n	22	16
	Mean ± SD	41.47 ± 15.352	60.48 ± 25.217
	Median	37.80	57.20
	Minimum - Maximum	21.0 – 74.8	24.2 – 97.6
Treatment cycle 4	n	18	16
	Mean ± SD	48.22 ± 21.288	41.45 ± 21.822
	Median	37.40	33.00
	Minimum - Maximum	22.0 – 102.8	21.4 – 82.2
Treatment cycle 5	n	15	12
	Mean ± SD	45.83 ± 18.473	45.00 ± 35.896
	Median	42.00	25.10
	Minimum - Maximum	21.6 – 80.6	21.0 – 116.8
Treatment cycle 6	n	14	9
	Mean ± SD	48.69 ± 24.076	37.78 ± 23.227
	Median	39.10	24.00
	Minimum - Maximum	24.4 – 107.0	21.0 – 88.4

Source: Text Table 8, a07545.pdf, pp 74

Table 52 shows the change from baseline by treatment arm in each TP. The difference between treatment arms on the mean scores over the two run-in cycles preceding TP1 was not statistically significant (p=0.71), but the difference between baseline (i.e., washout period) scores at TP2 was statistically significant (p=0.006), with the group previously (initially) exposed to DRSP/EE having a lower score than those who previously received placebo.

In both the DRSP/EE→placebo and placebo→DRSP/EE groups, the within group 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 treatment 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 52 DRSPS Scores: Baseline and Change from Baseline by Treatment and Cycle

Treatment Period 1	Statistic	Run-in Cycle 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				
Treatment Period 2	Statistic	Washout average	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: Table 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 in the modified ITT population 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 TP. Her results demonstrated a difference between DRSP/EE and placebo in 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.

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 305141 (difference at Cycle 1 collapsed over both treatment periods) of -12.4, was statistically significant (p=0.02).

Medical Reviewer's Comment:

- *The magnitude of the difference in treatment response between arms at the first cycle in both studies suggests that the efficacy results were not attributable to a possible compromise in blinding.*

10.2.8.4 Secondary Efficacy Endpoint Analysis

Secondary variables were analyzed only using the full analysis set. The secondary endpoints, computed at the baseline and end of treatment visits within each treatment period, were:

- Change from baseline in the average over three treatment cycles of the three functional impairment items of the DRSPS (Items 22-24 in Table 26).
- Change from baseline in the four CGI scores (interviewer-rated severity of illness, efficacy index and global improvement, and subject-rated global improvement) and number of responders according to the efficacy index
- Change from baseline in the physical and mental summary scales from the SF-36
- Change from baseline in the total score of the first 14 items, the score of medication satisfaction and the score of overall life satisfaction on the Q-LES-Q
- Change from baseline in the PMTS observer and self-rated scales
- Change in body weight: from baseline to end of treatment for each treatment period, between 1st-2nd treatment cycles, and between 2nd-3rd treatment cycles

DRSPS Functional Impairment

For the functional impairment items on the DRSPS, the average score over the last five days preceding menses was calculated for each item. On each item, the scale ranged from 1 (not at all) to 6 (extreme), with lower scores indicating improvement in symptomatology. The change from baseline score (averaged over the two run-in cycles for TP1 and based on the washout cycle for TP2) to treatment score (averaged over the three treatment cycles in each Treatment Period) was compared between treatment arms.

Baseline scores and changes from baseline in each treatment arm for the three functional impairment items are displayed in Table 53 to Table 55. The mean baseline scores on Items 22, 23 and 24 were similar between treatment sequences, while at washout the mean score in subjects who had received placebo was marginally significantly higher than those previously treated with DRSP/EE.

Table 53 Reduction of Productivity Score & Change from Baseline by Treatment Sequence and Cycle

| Statistic | DRSP/EE→placebo | | | Placebo→DRSP/EE | | | |
	N	Mean (SD)	p value for change from baseline	N	Mean (SD)	p value for change from baseline	Between-group p value
Baseline average	26	3.77 (1.0)	--	23	3.41 (1.1)	--	0.22
Cycle 1	26	1.96 (1.0)	**<0.00001**	23	2.43 (1.3)	**0.014**	
Cycle 2	26	1.98 (1.1)	**<0.00001**	20	2.46 (1.5)	**0.019**	
Cycle 3	25	1.94 (1.0)	**<0.00001**	18	2.56 (1.2)	**0.013**	
TP 1 average	26	1.96 (0.7)	**<0.00001**	23	2.43 (1.1)	**0.005**	
Washout	22	1.91 (1.1)	--	16	2.56 (1.6)	--	0.09
Cycle 4	18	2.44 (1.4)	**0.012**	16	2.15 (1.4)	**0.018**	
Cycle 5	15	2.65 (1.4)	0.071	12	2.15 (1.7)	0.362	
Cycle 6	14	2.49 (1.4)	0.091	9	1.98 (1.5)	0.221	
TP 2 average	18	2.50 (1.2)	**0.004**	16	2.05 (1.4)	0.062	

Bolded p values are statistically significant
Source: Table 23 & 24, a07545.pdf, Section 14, pp 177-180

Table 54 Interference with Social Activities Score & Change from Baseline by Treatment Sequence and Cycle

| Statistic | DRSP/EE→placebo | | | Placebo→DRSP/EE | | | |
	N	Mean (SD)	p value for change from baseline	N	Mean (SD)	p value for change from baseline	Between-group p value
Baseline average	26	3.81 (1.0)	--	23	3.40 (1.3)	--	0.16
Cycle 1	26	1.87 (1.1)	**<0.00001**	23	2.35 (1.2)	**0.008**	
Cycle 2	26	2.06 (1.2)	**<0.00001**	20	2.39 (1.4)	**0.009**	
Cycle 3	25	1.77 (0.8)	**<0.00001**	18	2.38 (1.1)	**0.005**	
Cycle 1-3 average	26	1.91 (0.7)	**<0.00001**	23	2.33 (1.0)	**0.002**	
Washout	18	1.92 (1.1)	--	16	2.64 (1.4)	--	0.06
Cycle 4	18	2.40 (1.4)	**0.007**	16	2.01 (1.4)	**0.037**	
Cycle 5	15	2.33 (1.3)	0.284	12	2.20 (1.7)	0.402	
Cycle 6	14	2.47 (1.5)	0.107	9	1.93 (1.0)	0.124	
Cycle 4-6 average	18	2.35 (1.2)	**0.041**	16	1.93 (1.2)	**0.034**	

Source: Table 26 & 27, a07545.pdf, Section 14, pp 182-185

Table 55 Interference with Relationships Score & Change from Baseline by Treatment Sequence and Cycle

Statistic	DRSP/EE→placebo			Placebo→DRSP/EE			
	N	Mean (SD)	p value for change from baseline	N	Mean (SD)	p value for change from baseline	Between-group p value
Baseline average	26	3.96 (1.0)	--	23	3.72 (1.0)	--	0.28
Cycle 1	26	1.97 (1.3)	**<0.00001**	23	2.36 (1.2)	**0.003**	
Cycle 2	26	1.87 (1.2)	**<0.00001**	20	2.51 (1.5)	**0.019**	
Cycle 3	25	1.77 (0.8)	**<0.00001**	18	2.50 (1.2)	**0.001**	
Cycle 1-3 average	26	1.88 (0.7)	**<0.00001**	23	2.39 (1.1)	**0.001**	
Washout	18	2.10 (1.2)	--	16	2.94 (1.5)	--	0.09
Cycle 4	18	2.43 (1.4)	0.221	16	1.85 (1.3)	**0.012**	
Cycle 5	15	2.28 (1.4)	0.605	12	2.20 (1.6)	0.143	
Cycle 6	14	2.17 (1.3)	0.390	9	1.73 (1.1)	**0.035**	
Cycle 4-6 average	18	2.36 (1.2)	0.204	16	1.86 (1.1)	**0.013**	

Source: Table 28 & 29, a07545.pdf, Section 14, pp 186-189

Medical Reviewer's Comments:

- *During TP1, both treatment arms showed statistically significant change from baseline at each cycle, on all three DRSPS functional measures. In TP2, results are difficult to interpret due to the difference in "baseline" measured at the washout cycle. However, the change from baseline in the subjects receiving placebo in TP2 never reached statistical significance, while for those subjects receiving DRSP/EE, the change from baseline was statistically significant at Cycles 4 and 6 and averaged over Cycles 4-6.*

The difference between in response between treatment arms was computed from the ANOVA model that included terms for sequence, period, treatment and center, collapsed over treatment period (i.e., scores from all subjects while taking DRSP/EE, regardless of whether it occurred in TP1 or TP2, were compared to scores from all subjects while taking placebo, see Table 56).

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Table 56 Results on Functional Impairment Items of DRSPS

		DRSP/EE (N = 54)	Placebo (N = 49)	
Item 22 Reduction of Productivity	n	42	41	
	Adjusted Mean	-1.205	-0.185	
	Difference [1]			-1.019
	P-Value [2]			0.0004
	95% Confidence Limits			-1.548,-0.491
Item 23 Interference with Social Activities	n	42	41	
	Adjusted Mean	-1.333	-0.333	
	Difference [1]			-1.000
	P-Value [2]			0.0002
	95% Confidence Limits			-1.491,-0.509
Item 24 Interference with Relationships	n	42	41	
	Adjusted Mean	-1.628	-0.561	
	Difference [1]			-1.067
	P-Value [2]			0.0002
	95% Confidence Limits			-1.577,-0.558

[1] The difference in adjusted treatment means (i.e. DRSP/EE minus placebo).
[2] P-value from ANOVA model with terms for sequence, period, treatment, and center, subject as random.

Source: Table 25, Section 14, a07545.pdf, p 181

The change from baseline seen with DRSP/EE treatment (-1.21) was statistically significantly greater than that seen with placebo treatment (-0.19) (p=0.0004) for Item 22, Reduction in Productivity. For Item 23, Interference with Social Activities, the change from baseline seen with DRSP/EE treatment (-1.33) was statistically significantly greater than that seen with placebo treatment (-0.33) (p=0.0002). For Item 24, Interference with Relationships, the change from baseline seen with DRSP/EE treatment (-1.62) was statistically significantly greater than that seen with placebo treatment (-0.56), p=0.0002).

Medical Reviewer's Comments:

- *A statistically significant difference between DRSP/EE and placebo in change from baseline on the three DRSPS secondary outcome measures was demonstrated when treatment assignments were collapsed over treatment periods.*

CGI Scores

The responses on the CGI parameters were based on subjects' status at the end of treatment Cycle 3 (Visit 7) in TP1 and at treatment Cycle 6 (Visit 11) in TP2. A last observation carried forward (LOCF) approach was used to impute missing data with scores from the most recent on-treatment data within a given Treatment Period. For the severity of illness parameter, change from baseline was assessed, with baseline data for TP1 obtained from Visit 4 (beginning of treatment Cycle 1), or earlier if Visit 4 data were missing and this assessment had been done out of the usual window. Baseline data for TP2 was obtained at Visit 8 (beginning of treatment Cycle 4) or based on Visit 4 or earlier data if Visit 8 was missing. On the severity of illness parameter, rated from 0 (normal) to 7 (among the most extremely ill patients), baseline and washout scores were comparable between treatment arms, and subjects in the DRSP/EE group demonstrated statistically significant improvements from baseline at the last treatment cycle in each treatment period (p = 0.0001 at TP1, p=0.015 at TP2). Subjects receiving placebo had

statistically significant improvements from baseline only at TP1 (p=0.006). The ANCOVA-estimated mean change from baseline in the DRSP/EE group, collapsed over treatment sequence, was statistically significantly different from that in the placebo group (p=0.012).

The efficacy index parameter was computed by dividing the therapeutic score by the side effect score, each ranging from 1 (lowest) to 4 (highest). Efficacy index scores could range from 0.25 (therapeutic effect unchanged or worse and side effects outweigh therapeutic effect) to 4 (therapeutic effect marked, vast improvement and side effects absent). Efficacy index scores and number of responders were assessed. A responder was defined as one having a therapeutic score of "marked" or "moderate" (3 or 4) with a side effect score of "none" or "do not significantly interfere with subject's functioning" (1 or 2). The efficacy index score rose in the DRSP/EE arm in TP1, and in both treatment arms in TP2; the ANCOVA-estimated mean change from baseline in the DRSP/EE group differed statistically significantly from that in the placebo group (p=0.017). The responder analysis based on the efficacy index also demonstrated a statistically significant difference favoring DRSP/EE in the proportion of responders in each treatment arm (p=0.004).

Global improvement was rated on a scale of 1 (very much improved) to 7 (very much worse). For both the investigator-rated and subject-rated scores, the mean improvement was greater in the DRSP/EE group, and this level reached statistical significance (p=0.011) in the investigator rating of global improvement. The difference in the self-rated scores was of borderline significance (p=0.052).

Medical Reviewer's Comments:
- *Analyzed with treatment assignment collapsed over treatment sequence, there was statistically significant evidence of improvement with DRSP/EE treatment on three of the four CGI investigator-rated global improvement measure, and a favorable trend of borderline significance on the fourth.*

SF-36 Scores

The SF-36 baseline for TP1 was obtained at Visit 4 or Visit 2 if the later data were not available. The baseline for TP2 was obtained at Visit 8, or Visit 4 (or Visit 2 if unavailable) if Visit 8 were missing. Responses for the treatment periods were obtained at Visit 7 (end of treatment Cycle 3) for TP1 and at Visit 11 (end of treatment Cycle 6) for TP2. Missing visit scores were replaced by scores imputed by LOCF within the same Treatment Period. Eight subscales and one item of self-reported health change were computed from the 36 items on the questionnaire; since the responses ranges varied across items, the items were recoded and transformed to a 0-100 scale. From the 8 subscales, two summary scales, mental and physical, were computed and change from baseline to EOT for each treatment period was compared across treatment arms.

Baseline scores for both the physical and mental subscales were comparable across treatment arms in TP1; in TP2, the mental subscale was significantly higher at washout in the DRSP/EE→placebo group. Improvement from baseline on the mental subscale was statistically significant in the subjects receiving DRSP/EE group at either treatment period. On the physical subscale, the only statistically significant improvement was in the subjects receiving placebo at TP2. However, the change in either subscale was not statistically significantly different between the treatment arms collapsed over treatment sequence.

Q-LES-Q Scores

The Q-LES-Q was also evaluated for change from baseline (Visit 4 for TP1, Visit 8 for TP2) to EOT within each treatment period (Visit 7 for TP1, Visit 11 for TP2) over three parameters (first 14 items, medication and overall life satisfaction) over the two treatment arms. The first 14 items were rated from 1 (very poor) to 5 (very good); the sum of these 14 scores was then expressed as a percent of the maximum possible score. Baseline and washout values were comparable between treatment arms, both

groups showed significant improvement from baseline to EOT at TP1 only. The improvement from baseline, compared between treatment arms collapsed over treatment sequence, was statistically significant favoring DRSP/EE (p=0.045).

Satisfaction with medication and overall life satisfaction were each single items, rated on the same 1-5 scale. Medication satisfaction was assessed only at the end of treatment. Subjects assigned to the DRSP→placebo sequence had slightly higher scores at the end of TP1 than at TP2, while subjects in the placebo →DRSP/EE sequence had similar scores at both treatment periods. Collapsed over treatment period, the difference between treatment arms was not statistically significantly. For overall life satisfaction, baseline and washout values did not differ significantly between treatment arms, both of which showed statistically significant improvement from baseline at TP1 only. The ANCOVA analysis, comparing treatment arms collapsed over treatment sequence, was statistically significantly in favor of DRSP/EE treatment (p=0.044).

Medical Reviewer's Comment:

- ***Analyzed with treatment assignment collapsed over treatment sequence, there was statistically significant evidence of improvement with DRSP/EE treatment on the first 14 items of the Q-LES-Q and on overall life satisfaction.***

PMTS Scores

The two PMTS scales were scored differently, but each provided a score ranging from 0-36. The subject-rated scale obtained "yes/no" responses to 36 symptoms, while the investigator-rated scale rated eight symptoms from 0-4 and two symptoms from 0-2. Change from baseline (Visit 4 preferentially, or Visit 2 for TP1; Visit 8 preferentially, or Visit 4 if missing for TP2) to EOT for each treatment period (Visit 7 or 11) was compared between treatment groups. For both the observer-rated and the self-rated scales, baseline scores were comparable across treatment arms at TP1, but were statistically significantly higher in the placebo→DRSP/EE sequence at TP2. Both groups showed statistically significant changes from baseline on both scales at TP1, but only the placebo→DRSP/EE sequence was significantly improved, on both scales, at TP2. The difference between treatment arms collapsed over treatment period was statistically significant in favor of DRSP/EE on both scales (p=0.041 for the observer-rated, p=0.010 for the self-rated scale).

Body Weight

Changes in body weight over treatment were compared between treatment arms, with baseline obtained at Visit 4 for TP1 and Visit 8 for TP2, and EOT weight measured at the last visit for each treatment period. Weight change between the first and second cycles and second and third cycles in TP1 was also assessed. The baseline and washout weights did not differ significantly between treatment sequences. Collapsed over treatment sequence, the subjects receiving DRSP/EE generally displayed very minor decreases in weight over treatment, with the placebo subjects showing minor increases; however, this difference was not statistically significant.

Medical Reviewer's Comment:

- ***No significant effect of DRSP/EE on weight or weight loss was demonstrated.***

10.2.9   Safety

10.2.9.1 Safety Measurements

All participants who received at least one dose of study medication were included in the summaries and listings of safety data (N=103). Adverse events were monitored from Visit 2 until the final study visit with the exception of pregnancy, which was followed until conclusion. In addition to spontaneous

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reports, adverse events were elicited at each visit by a general question about any health problems beyond usual PMDD symptoms. 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 Hoecht 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 (at run-in, washout [exams only] and EOT visits)
- Vital signs (at all clinic visits)
- Laboratory assessment (hematology, serum chemistries including potassium levels, thyroid [at run-in, washout and EOT visits 2 only], hepatic and lipid panels, done at run-in, treatment Cycle 2, washout, treatment Cycle 5 and EOT visits, and urinalysis, done at run-in, washout and EOT
- In addition to adverse events generally, selected cardiovascular (arrhythmia, brady/tachycardia, dizziness, palpitations and syncope) and thromboembolic events were evaluated

Medical Reviewer's Comment:

- **The definition of SAEs did not include cancers; however, none occurred.**

Laboratory measures, vital signs and parameters from physical examination were assessed by summary statistics comparing baseline values with post-baseline values for active treatment and placebo periods. Shifts between categories of low, normal or high or normal/abnormal 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 and ≥ 6.0 mEq/L was tabulated by treatment, and the proportions in each category compared statistically between treatment arms. Change from baseline to the last treatment cycle in each treatment period in serum K^+, maximum serum K^+, serum creatinine, and creatinine clearance was compared by ANCOVA with terms for effects due to treatment and center, and baseline value as a covariate.

10.2.9.1.1 Extent of exposure

Exposure to study drug for the two treatment arms is displayed in Table 57. A full three cycles in either treatment period would entail 72 days of drug exposure or 84 days of treatment.

Table 57 Exposure by Treatment Group

Duration of Treatment (days)	DRSP/EE (N = 54)	Placebo (N = 49)
N [a]	47	44
Mean ± Standard Deviation	71.6 ± 23.36	76.6 ± 21.43
Median	82.0	82.0
Minimum – Maximum	3 – 91	18 – 140 [b]

[a] 7 subjects receiving DRSP/EE were lost to F/U; 4 subjects receiving placebo were lost to F/U and one has status unknown
[b] The 140 day exposure period was entered for a subject who took placebo for 9 days, stopped for 47 days due to an adverse event, then resumed taking placebo for 81 days
Source: Text Table 33, a07545.pdf, p 107

10.2.9.2 Adverse Events

10.2.9.2.1 Serious adverse events

Deaths: There were no deaths in the trial.

Premature termination due to adverse events: Four subjects (7.4%) terminated prematurely from the study during exposure to DRSP/EE because of one or more adverse events, as did two subjects (4.1%) during exposure to placebo. All adverse events leading to withdrawals are listed in Table 58.

Medical Reviewer's Comment:

- *An additional subject (#80001) was discontinued at the Applicant's request due to elevated potassium levels during DRSP/EE treatment, which had normalized by a follow-up blood draw one month later. She experienced no cardiovascular adverse events. The investigator did not consider the elevations in K^+ to be clinically relevant, but the Applicant requested that she be withdrawn; therefore, she was listed as withdrawn at Applicant's request, not due to an adverse event. The subject had had an elevated run-in K^+ of 5.5 mEq/L. This was attributed to procedural error, and rechecked two weeks later, at which time it was 4.2 mEq/L. During treatment with DRSP/EE treatment, her K^+ was 5.3 mEq/L at Cycle 2, rising to 5.6 mEq/L at the Washout Visit. A follow-up blood draw one month later showed a level of 5.4 mEq/L.*

- *An additional subject in the placebo→DRSP/EE group was listed as withdrawn due to an adverse effect; 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.*

Table 58 Adverse Events Associated with Treatment Withdrawals

Preferred Term	During DRSP/EE Treatment N=54		During Placebo Treatment N=49	
	N	%	N	%
Total Number of Subjects	4	7.4	2	4.1
Nausea	2	3.7	1	2.0
Nervousness	2	3.7	1	2.0
Breast tenderness	1	1.9	0	0
Dysmenorrhea	1	1.9	0	0
Emotional lability	1	1.9	0	0
Incoordination	1	1.9	0	0
Vomiting	1	1.9	0	0
Migraine	0	0	1	2.0
Pregnancy	0	0	1	2.0
Sweating	0	0	1	2.0

Number of events exceed number of withdrawals, because some subjects experienced multiple events
Source: Table 91, Section 14, a07545.pdf, p 307

Serious adverse events: There was a single subject who experienced a serious adverse event (SAE) of miscarriage during the placebo treatment period, listed in Table 59. Her pregnancy was diagnosed 52 days after starting placebo; study medication was discontinued and the miscarriage occurred 7 days later. Thus, the overall rate of SAEs was 0% during DRSP/EE exposure and 2.0% during placebo exposure.

Table 59 Serious Adverse Events during Treatment

SAE (Subject #)	Treatment	Causality	Timing	Intensity	Resolution
Miscarriage (231002)	Placebo	Unrelated	59 days after starting placebo	Severe	Recovered

Source: Table 90, a07545.pdf, Section 14, p 306

10.2.9.2.2 Frequent adverse events

At least one adverse event was reported by 76% and 61%) of the subjects during their exposure to DRSP/EE and placebo, respectively. Events occurring at ≥ 10% frequency during DRSP/EE exposure were:

- Nausea (18.5%)
- Upper respiratory infection (16.7%)
- Headache (14.8%)
- Intermenstrual bleeding (14.8%)
- Breast pain (11.1%)

Events occurring at ≥ 10% frequency during exposure to placebo were:

- Headache (14.3%)
- Nausea (10.2%)

Overall adverse events occurring with frequency ≥2% are reported in Table 60. Body systems with increased frequency of clusters of adverse events in subjects during their exposure to DRSP/EE as compared to placebo were:

- Digestive/Gen, primarily due to increased rates of nausea (18.5% vs. 10.0%)
- Nervous/CNS, primarily due to increased frequency of incoordination and nervousness (13.0% vs. 4.1%)
- Skin/breast, due to increased rates of breast pain (11.1% vs. 4.1%)
- Urogenital/female genitalia/menstrual, primarily due to increased rates of intermenstrual bleeding and menstrual disorder (20.4% vs. 2.0%)

Medical Reviewer's Comment:

- ***Several adverse events seen more commonly in the DRSP/EE group (breast and menstrual disorders, nervousness and nausea) represent adverse events commonly reported with oral contraceptives and discussed in the labeling for Yasmin.***

The frequency of adverse events considered by the Applicant to be drug-related was higher for those events occurring during DRSP/EE exposure (48% vs. 29% for events occurring during placebo exposure). Among the clusters of symptoms that were more common in DRSP/EE subjects, similar proportions of nausea, nervousness and incoordination, and menstrual disorders were considered drug-related in each group (8 of 10 cases of nausea during DRSP/EE vs. 4 of 5 cases during placebo treatment; 5 of 6 cases of nervousness or incoordination during DRSP/EE vs. 2 of 2 cases during placebo treatment; 9 of 11 menstrual disorders in DRSP/EE subjects vs. 1 of 1 in placebo subjects). Slightly fewer events of breast pain were considered drug-related when experienced during DRSP/EE exposure (2 of 6) as compared to those experienced during placebo treatment (1 of 2).

Table 60 Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects

Adverse Event	During DRSP/EE Exposure N=54		During Placebo Exposure N=49	
	N	%	N	%
Nausea	10	18.5	5	10.2
URI	9	16.7	3	6.1
Intermenstrual bleeding	9	16.7	1	2.0
Headache	8	14.8	7	14.3
Breast pain	6	11.1	2	4.1
Nervousness	5	9.3	2	4.1
Asthenia	4	7.4	4	8.2
Back pain	3	5.6	1	2.0
Dysmenorrhea	3	5.6	2	3.7
Menstrual disorder	3	5.6	0	0
Vaginitis	2	3.7	2	4.1
Weight loss	2	3.7	2	4.1
Alopecia	2	3.7	1	2.0
Cloasma	2	3.7	1	2.0
Hyperlipemia	2	3.7	1	2.0
Migraine	2	3.7	1	2.0
Sore throat	2	3.7	1	2.0
Incoordination	2	3.7	0	0
Libido decreased	2	3.7	0	0
Pain in extremity	2	3.7	0	0
Tooth disorder	1	1.9	5	10.2
Accidental injury	1	1.9	4	8.2
Pain	1	1.9	3	6.1
Abdominal pain	1	1.9	2	4.1
Emotional lability	1	1.9	2	4.1
Dizziness	1	1.9	1	2.0
Gastroenteritis	1	1.9	1	2.0
UTI	1	1.9	1	2.0
Vomiting	1	1.9	1	2.0
Sinusitis	0	0	3	6.1

Source: Text Table 34, a07545.pdf, p 109

10.2.9.3 Cardiovascular and Thromboembolic Events

Due to the potential potassium-sparing effect of drospirenone, the Applicant specifically surveyed adverse events that might be associated with hyperkalemia (arrhythmia, bradycardia, dizziness, palpitation, syncope and tachycardia). The only adverse events in this category that occurred were two cases of dizziness. One subject had a near-syncopal episode the day after her first dose of DRSP/EE. Her serum potassium ranged between 3.9-4.6 mEq/L over the course of the trial (normal range 3.4-5.4 mEq/L). A second subject experienced intermittent dizzy spells while taking placebo. Her serum potassium ranged between 4.2-4.8 mEq/L over the course of the trial.

No subject experienced a thromboembolic event during either treatment period.

Medical Reviewer's Comment:

- ***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.***

10.2.9.4 Laboratory Values and Urinalysis

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

Hematology

No subject had an adverse event reported relating to hematologic values.

Selected mean and median values at baseline, treatment Cycle 2, washout, treatment Cycle 5 and at the final EOT visit (or at the time of early withdrawal) are presented in Table 61. The mean and median changes from baseline were small and similar following exposure to either drug. Shift tables showed that only a single DRSP/EE→placebo subject shifted from a normal hemoglobin value at baseline/washout to a low value (Treatment Cycle 5), when she was exposed to placebo. Two subjects in the placebo→DRSP/EE arm shifted into the low hemoglobin category, one during each drug exposure. No subject in either arm shifted into the low value category for hematocrit or platelets.

Table 61 Hematology Values: Mean (SD) and Median by Treatment Group

Lab Test		DRSP/EE->Placebo			Placebo->DRSP/EE		
		N	Mean (SD)	Median	N	Mean (SD)	Median
Hematocrit (%)	Baseline	33	41.5 (3.1)	41.2	30	40.9 (3.1)	41.5
	Tx Cycle 2	27	40.0 (2.6)	40.4	24	39.6 (3.0)	39.8
	EOT Period 1	29	40.6 (3.1)	40.5	26	39.8 (3.0)	40.2
	Tx Cycle 5	17	40.1 (2.9)	39.7	13	37.9 (3.7)	37.6
	EOT Period 2	19	39.8 (2.8)	40.2	16	39.3 (3.6)	39.8
Hemoglobin (g/dL)	Baseline	33	13.4 (0.9)	13.2	30	13.2 (1.3)	13.4
	Tx Cycle 2	27	13.0 (0.9)	12.9	24	12.8 (1.2)	13.1
	EOT Period 1	29	13.2 (0.8)	13.2	26	12.8 (1.3)	13.1
	Tx Cycle 5	17	13.1 (1.0)	13.2	13	12.5 (1.6)	12.5
	EOT Period 2	19	13.1 (0.9)	13.0	16	12.8 (1.5)	13.3
Platelets (10⁹/L)	Baseline	33	286.2 (74.1)	279.0	30	277.5 (65.8)	274.5
	Tx Cycle 2	27	295.7 (71.7)	285.0	23	294.2 (72.1)	293.0
	EOT Period 1	29	311.5 (73.4)	306.0	26	297.1 (69.4)	290.5
	Tx Cycle 5	17	289.0 (45.9)	288.0	13	282.6 (67.2)	273.0
	EOT Period 2	19	283.4 (58.0)	277.0	16	293.3 (73.1)	276.5

EOT = Visit 7 (TP1), Visit 11 (TP2) or end of treatment visit if subject terminated prematurely
Source: Table 93, a07545.pdf, Section 14, pp 325-34

Data on change from baseline, analyzed by drug exposure regardless of treatment sequence, are presented in Table 62.

Table 62 Hematology Values: Mean (SD) & Median Change from Baseline by Drug Exposure

Lab Test		N	Mean (SD)	Median	N	Mean (SD)	Median
			DRSP/EE			**Placebo**	
Hematocrit (%)	Baseline	44	40.78 (2.77)	40.5	45	40.34 (2.75)	40.4
	Change @ Last Tx Cycle on Drug	44	-1.25 (2.51)	-0.95	45	-0.36 (2/41)	-0.20
Hemoglobin (g/dL)	Baseline	44	13.18 (1.04)	13.2	45	13.04 (1.04)	13.2
	Change @ Last Tx Cycle on Drug	44	-0.33 (0.72)	-0.20	45	-0.11 (0.57)	-0.10
Platelets (10^9/L)	Baseline	44	286.0 (69.43)	280.0	45	286.0 (69.86)	278.0
	Change @ Last Tx Cycle on Drug	44	5.14 (39.06)	0	45	6.16 (39.20)	93.0

Source: Table 97, a07545.pdf, Section 14, pp 365-74

Medical Reviewer's Comments:

- *Overall, changes in hematologic variables were minimal. However, looking across treatment sequence, it appears that subjects had slightly greater mean decreases from baseline in hemoglobin and hematocrit during their exposure to DRSP/EE than to placebo.*

Chemistry

General Chemistry

A total of three subjects had abnormal postbaseline chemistry values considered to be clinically relevant. One subject had elevated AST and ALT values that were outside the normal range and judged to be clinically relevant. She had normal values at run-in, during TP1, in which she received placebo, and at washout. During treatment with DRSP/EE, her AST rose to 54 IU/L (range 0-37 IU/L) and her ALT rose to 68 IU/L (range 0-47 IU/L). She continued treatment and her AST resolved within one month, while the ALT returned to the normal range by the end of treatment. The other two subjects are discussed below, in the Lipids section.

Selected chemistry and lipid values at baseline and over the course of treatment are displayed in Table 63 and Table 64.

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Table 63 Mean (SD) Chemistry Safety Variables

Lab Test		DRSP/EE->Placebo		Placebo->DRSP/EE	
		N	Mean (SD)	N	Mean (SD)
Creatinine (mg/dl)	Baseline	34	0.76 (0.12)	30	0.74 (0.15)
	Tx Cycle 2	27	0.79 (0.10)	23	0.76 (0.15)
	EOT Period 1	29	0.77 (0.13)	25	0.76 (0.12)
	Tx Cycle 5	17	0.75 (0.10)	13	0.78 (0.18)
	EOT Period 2	19	0.92 (0.80)	17	0.77 (0.14)
Potassium (mEq/L)	Baseline	34	4.39 (0.45)	30	4.32 (0.40)
	Tx Cycle 2	27	4.38 (0.43)	23	4.27 (0.32)
	EOT Period 1	29	4.38 (0.50)	25	4.29 (0.24)
	Tx Cycle 5	17	4.33 (0.54)	13	4.23 (0.37)
	EOT Period 2	19	4.42 (0.67)	17	4.14 (0.34)
Glucose (mg/dl)	Baseline	34	88.4 (12.6)	30	87.6 (9.2)
	Tx Cycle 2	27	85.7 (10.7)	23	88.4 (11.5)
	EOT Period 1	29	88.8 (16.2)	25	88.6 (8.1)
	Tx Cycle 5	17	84.4 (9.4)	13	89.1 (12.6)
	EOT Period 2	19	86.1 (9.4)	17	86.3 (9.0)
AST (U/L)	Baseline	34	20.1 (4.8)	30	19.4 (5.0)
	Tx Cycle 2	27	18.8 (3.4)	23	21.2 (6.9)
	EOT Period 1	29	19.8 (3.2)	25	21.0 (6.9)
	Tx Cycle 5	17	24.2 (11.6)	13	19.1 (5.0)
	EOT Period 2	19	20.5 (4.3)	17	18.4 (4.0)
ALT (U/L)	Baseline	33	16.4 (4.8)	30	19.3 (6.7)
	Tx Cycle 2	27	15.4 (3.9)	23	18.1 (4.6)
	EOT Period 1	29	15.8 (4.6)	25	21.3 (10.3)
	Tx Cycle 5	17	23.2 (17.9)	13	16.6 (4.6)
	EOT Period 2	19	19.2 (6.4)	17	17.1 (5.7)
Alk Phos (U/L)	Baseline	34	68.2 (23.1)	30	69.0 (22.0)
	Tx Cycle 2	27	57.1 (18.7)	23	66.8 (21.8)
	EOT Period 1	29	63.1 (20.1)	25	67.2 (22.2)
	Tx Cycle 5	17	72.0 (24.7)	13	56.4 (16.2)
	EOT Period 2	19	67.7 (24.3)	17	56.0 (14.0)
Total Bili (mg/dl)	Baseline	33	0.48 (0.28)	30	0.43 (0.20)
	Tx Cycle 2	27	0.42 (0.26)	23	0.40 (0.14)
	EOT Period 1	29	0.37 (0.23)	25	0.40 (0.20)
	Tx Cycle 5	17	0.52 (0.36)	13	0.32 (0.16)
	EOT Period 2	19	0.53 (0.34)	17	0.35 (0.20)

EOT = Visit 7 (TP1), Visit 11 (TP2) or end of treatment visit if subject terminated prematurely
Source: Table 99, a07545.pdf, Section 14, p 385-408

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Table 64 Mean (SD) Serum Lipid Variables

Total Cholesterol (mg/dl)	Baseline	34	185.7 (34.6)	30	184.9 (26.2)
	Tx Cycle 2	27	190.9 (31.0)	23	179.6 (29.0)
	EOT Period 1	29	210.3 (38.1)	25	178.8 (29.3)
	Tx Cycle 5	17	184.6 (25.6)	13	194.5 (30.8)
	EOT Period 2	19	181.7 (24.2)	17	196.6 (34.7)
HDL Cholesterol (mg/dl)	Baseline	33	60.7 (14.2)	30	58.9 (15.9)
	Tx Cycle 2	27	67.9 (15.8)	23	57.6 (16.8)
	EOT Period 1	29	67.3 (16.6)	25	57.4 (15.4)
	Tx Cycle 5	17	58.8 (12.9)	13	59.8 (16.3)
	EOT Period 2	19	58.0 (12.3)	17	59.2 (13.6)
LDL Cholesterol (mg/dl)	Baseline	33	105.7 (28.7)	30	106.5 (28.9)
	Tx Cycle 2	27	100.1 (28.3)	23	101.7 (24.1)
	EOT Period 1	29	114.2 (31.0)	25	102.2 (28.2)
	Tx Cycle 5	17	107.3 (23.9)	12	104.5 (24.5)
	EOT Period 2	19	105.7 (23.6)	17	111.0 (25.5)
Triglycerides (mg/dl)	Baseline	33	97.7 (63.5)	30	97.7 (57.6)
	Tx Cycle 2	27	114.0 (71.0)	23	101.3 (73.7)
	EOT Period 1	29	130.4 (89.4)	25	94.9 (60.8)
	Tx Cycle 5	17	92.3 (71.2)	13	144.5 (108.3)
	EOT Period 2	19	90.1 (52.2)	17	131.5 (87.9)

EOT = Visit 7 (TP1), Visit 11 (TP2) or end of treatment visit if subject terminated prematurely
Source: Table 99, a07545.pdf, Section 14, p 385-408

Creatinine and Creatinine Clearance
A single DRSP/EE→placebo subject (#80039) experienced an elevated creatinine level of 4.2 mg/dl, which occurred at the EOT visit, following placebo exposure. This was accompanied by a potassium level of 6.2 mEq/L (normal range 3.6-5.2 mEq/L) and a creatinine clearance of 27.6 ml/min. The values were confirmed on a repeat analysis; however, the subject had been in the normal range on these parameters at all previous sampling periods, and returned to normal values six days later. The ANCOVA estimated mean creatinine for treatment with DRSP/EE at EOT did not differ statistically significantly from that seen following placebo treatment.

Creatinine clearance was calculated using the standard formula for females. At baseline, four subjects showed mild renal impairment (creatinine clearance >50 and ≤80 ml/min) and during treatment, Subject #80039, noted above, had values indicating severe renal impairment with a creatinine clearance of 27.6 ml/min. Mean and maximum on-treatment potassium levels were similar in subjects with exposed to either drug who had mild renal impairment at baseline as compared to subjects with normal baseline creatinine clearance. There was not a statistically significant difference between drug exposures in mean creatinine clearance at the end of treatment period; however, the difference from baseline at the end of treatment period was greater with DRSP/EE exposure (-6.1 ml/min) as compared to placebo exposure (-4.1 ml/min).

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

Potassium levels changed minimally over treatment, showing median changes ranging from -0.1 to 0.2 mEq/L over both treatment arms, and a maximum mean increase of 0.12 mEq/L, which occurred in the DRSP/EE→placebo group during placebo exposure. Differences between treatment arms in mean potassium at end of treatment period were not statistically significant. The maximal potassium value on treatment was 6.2 mEq/L, occurring in a single subject in the DRSP/EE→placebo group during placebo exposure. One subject while taking DRSP/EE and two while taking placebo (one was Subject #80039 above) had potassium levels above 5.4 mEq/L. Table 65 lists these three subjects with potassium levels above 5.4 mEq/L during treatment. None of the five subjects with these elevations in potassium experienced any of the selected cardiovascular events surveyed (see Section 10.1.9.3). The only value considered clinically relevant was in Subject #80001, in whom it was considered an adverse event.

Table 65 Listing of Subjects with Elevated Postbaseline Potassium Levels

Treatment	Subject #	Baseline Value (mEq/L)	Cycle 2 Value (mEq/L)	Washout Value (mEq/L)	Cycle 5 Value (mEq/L)	EOT Value (mEq/L)	Renal Function at high K^+ value
DRSP/EE→placebo	80021	5.2	5.2	5.2	5.7	Refused	Normal
	80039*					6.2	Severely impaired
	80001**	5.5 (redraw 4.2)	5.3	5.6			Normal

*Subject #80039 had levels six days later showing potassium level of 4.4 mEq/L and creatinine clearance in the normal range.
*Subject #80001 was discontinued at the Applicant's request prior to taking TP2 medication; a follow-up potassium level one month later was 5.4 mEq/L.
Source: 07545.pdf, pp 118-119

Table 66 displays the percent of subjects who experienced transitions in potassium levels with treatment. At Cycle 2, neither exposure group had any subjects shift from normal baseline potassium values to high. By the EOT for TP1, the DRSP/EE-exposed subjects had a greater frequency of shifts to high values (10.3% vs. 0% in placebo subjects). At Cycle 5, the placebo-exposed subjects had a higher proportion shifting to high values (11.8% vs. 0 in the DRSP/EE subjects. By the EOT for TP2, 10.5% of placebo subjects had shifts to high values, while still, no DRSP/EE subjects shifted to high values.

Medical Reviewer's Comment:

- *Even those subjects who shifted into the high range of potassium levels had relatively normal levels; as seen in Table 65, only 1 subject during or immediately following treatment with DRSP/EE had a serum potassium level greater than 5.4 mEq/L (i.e., 5.6 mEq/L). The maximum value observed in this study was 6.2 mEq/L, which occurred following treatment with placebo.*

Table 66 Transitions in Potassium Values with Treatment

Parameter	Treatment Cycle	Treatment Group	Baseline Value (%)	Low (%)	Normal (%)	High (%)	Total (%)
Potassium	Cycle 2	DRSP/EE→placebo	Low (%)	0	0	0	0
			Normal (%)	1 (3.7)	25 (92.6)	0	26 (96.3)
			High (%)	0	0	1 (3.7)	1 (3.7)
			Total (%)	1 (3.7)	25 (92.6)	1 (3.7)	27 (100)
		Placebo→DRSP/EE	Low (%)	0	1 (4.3)	0	1 (4.3)
			Normal (%)	0	21 (91.3)	0	21 (91.3)
			High (%)	0	1 (4.3)	0	1 (4.3)
			Total (%)	0	23 (95.6)	0	23 (95.6)
	EOT – TP1	DRSP/EE→placebo	Low (%)	0	0	0	0
			Normal (%)	0	25 (86.2)	3 (10.3)	28 (96.6)
			High (%)	0	0	1 (3.4)	1 (3.4)
			Total (%)	0	25 (86.2)	4 (13.7)	29 (100)
		Placebo→DRSP/EE	Low (%)	0	1 (4.0)	0	1 (4.0)
			Normal (%)	0	23 (92.0)	0	23 (92.0)
			High (%)	0	1 (4.0)	0	1 (4.0)
			Total (%)	0	25	0	25
	Cycle 5	DRSP/EE→placebo	Low (%)	0	0	0	0
			Normal (%)	0	15 (88.2)	2 (11.8)	17 (100)
			High (%)	0	0	0	0
			Total (%)	0	15 (88.2)	2 (11.8)	17 (100)
		Placebo→DRSP/EE	Low (%)	0	0	0	0
			Normal (%)	0	13 (100)	0	13 (100)
			High (%)	0	0	0	0
			Total (%)	0	13 (100)	0	13 (100)
	EOT – TP2	DRSP/EE→placebo	Low (%)	0	0	0	0
			Normal (%)	0	17(89.5)	2 (10.5)	19 (100)
			High (%)	0	0	0	0
			Total (%)	0	17(89.5)	2 (10.5)	19 (100)
		Placebo→DRSP/EE	Low (%)	0	1 (5.9)	0	1 (5.9)
			Normal (%)	0	16 (94.1)	0	16 (94.1)
			High (%)	0	0	0	0
			Total (%)	0	17 (100)	0	17 (100)

Source: Table 101, 07545.pdf, p 445

Lipids

Two subjects had lipid values that were outside the normal range and judged to be clinically relevant. One subject withdrew consent during the washout period following DRSP/EE treatment, and had an elevated triglyceride level of 328 mg/dl at the final visit (range 0-150 mg/dl) that was considered an adverse event. A second subject had an elevated total cholesterol value of 219 mg/dl (range 0-199 mg/dl) during treatment with DRSP/EE that was considered an adverse event. She had previously had elevated levels at run-in and during treatment with DRSP/EE (201 and 221 mg/dl, respectively) that were not reported as adverse events.

Medical Reviewer's Comment:

- *This reviewer concurs that the abnormal potassium, creatinine and creatinine clearance values obtained in Subject 80039 following placebo exposure were probably spurious.*
- *There was no evidence of significant hyperkalemia with DRSP/EE treatment, and, based on a small number of subjects, no evidence that mild renal impairment had an adverse impact on potassium levels during treatment.*
- *Liver enzymes were typically lower on treatment in the DRSP/EE group and showed a greater mean and median decrease from baseline over treatment.*
- *The mean cholesterol and triglyceride values during treatment are greater in the DRSP/EE group than in the placebo group, despite similar baseline values. No tests of significance are provided. The DRSP/EE group also showed increases from baseline over treatment in total cholesterol and triglycerides, while the placebo group decreased.*
- *Other laboratory values did not show notable change from baseline or difference between treatment groups.*

Urinalysis

Two DRSP/EE→placebo subjects had clinically relevant urinalysis findings. One (#80019) had findings consistent with a UTI at the washout cycle following DRSP/EE treatment; she was treated and completed the study. The second (#260037) withdrew consent and discontinued the trial during washout from DRSP/EE, with an elevated leukocyte value that was considered an adverse event. She also had a clinically relevant triglyceride value at her final visit, during washout. No other relevant changes in urinalysis parameters were noted on treatment.

10.2.9.5 Pregnancies

Three subjects became pregnant during the study. Subject 230012, in the DRSP/EE→placebo arm, became pregnant during TP2 (placebo) and experienced a miscarriage, which was classified as an SAE. Subject 200014, also in the DRSP/EE→placebo arm, had a pregnancy detected during washout, on 12/23/02. Her last day on DRSP/EE was 11/21/02 and her LMP was 11/23/02. She was discontinued from the study and lost to follow-up; pregnancy outcome is unknown. Subject 80004 was in the placebo→DRSP/EE group and had a pregnancy detected during washout, with a positive pregnancy test on 2/12/03. Her last day on placebo was 12/29/02 and her LMP was 1/3/03. She underwent an elective abortion one week following the pregnancy test.

Medical Reviewer's Comment:

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

10.2.9.6 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 67.

No cases of hypertension occurred in this trial.

Medical Reviewer's Comment:

- *There were no major changes in vital signs during treatment with either drug, and mean and median values were similar for the two groups, regardless of the treatment sequence. Only descriptive statistics were provided.*

Table 67 Mean (SD) Blood Pressure and Pulse by Treatment Period and Drug Exposure

Vital Sign	Treatment	Baseline	Cycle 2	Cycle 3	EOT
Systolic BP (mm Hg)	N	54	43	39	43
	DRSP/EE	109.6 (10.8)	111.2 (12.2)	109.5 (11.6)	107.9 (12.3)
	N	48	41	38	39
	Placebo	110.84 (10.1)	111.0(10.2)	110.0 (11.8)	109.7 (12.5)
Diastolic BP (mm Hg)	N	54	43	39	43
	DRSP/EE	70.3 (10.2)	72.0 (9.4)	71.6 (10.0)	70.6 (11.1)
	N	48	41	38	39
	Placebo	72.2 (9.5)	72.4 (9.2)	71.5 (10.3)	71.8 (9.9)
Pulse (BPM)	N	54	43	40	43
	DRSP/EE	70.4 (8.4)	69.3 (7.2)	72.5 (8.7)	71.7 (10.0)
	N	48	41	37	39
	Placebo	70.3 (8.1)	68.5 (10.2)	71.0 (9.3)	71.8 (9.0)

Source: Table 122, a07545.pdf, Section 16, p 594-6

10.2.9.7 Physical and Gynecological Examinations

Physical and gynecological exams, including Pap smear, were performed at run-in Cycle 2, washout and the EOT visits. Two subjects had changes on physical exam that were judged by the Applicant to be clinically significant. One subject experienced a fracture during placebo treatment; the other had back pain followed by a finding of leukocytes in the urinalysis during DRSP/EE treatment.

One subject had a clinically significant change in her gynecological exam - during TP2, when she was receiving DRSP/EE, she was noted to have cervicitis and vaginitis. She had also had cervicitis at baseline.

One subject had an abnormal Pap smear results subsequent to the baseline assessment; this occurred at the EOT assessment, following her DRSP/EE treatment, when she was noted to have a shift in vaginal flora consistent with bacterial vaginosis.

Medical Reviewer's Comment:

- *None of the changes on physical exam, gynecological exam or Pap smear in DRSP/EE subjects were judged by the reviewer to be drug-related.*

10.2.10   Reviewer's assessment of efficacy and safety

Efficacy

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

The ANCOVA results 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 a p-value of 0.006, when analyzed using the per protocol population.

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 of -14 (95% CI -25, -3, p=0.02) for TP1 and of -24.5 (-36, -13, p=0.001) for TP2.

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 305141 (difference at Cycle 1 collapsed over both treatment periods) of -12.4 was statistically significant (p=0.02). The magnitude of the difference in treatment response between arms at the first cycle in both studies suggests that the efficacy results were not attributable to a possible compromise in blinding.

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

- Change from baseline in the average over three treatment cycles of the three functional impairment items of the DRSPS (Items 22-24 in Table 26), with treatment assignment collapsed over treatment sequence.
- Change from baseline in three of four CGI scores (severity of illness, efficacy index, and interviewer-rated global improvement)
- Change from baseline in the total score of the first 14 items, and the score of overall life satisfaction, on the Q-LES-Q
- Change from baseline in the PMTS observer and self-rated scales

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

The Division had requested that the Applicant show that changes in symptomatology occurring with treatment were of clinical benefit to subjects, by providing a value for the minimally important clinical difference (MICD) between the responses of the treatment and placebo groups and by describing the method by which the MICD was determined. Although the Applicant did not provide an actual value for MICD, the estimated effect size, calculated by dividing the mean difference in response between treatment and placebo groups by the corresponding standard deviation (SD), was suggested as a proxy for MICD. By convention[1], effect sizes of 0.2, 0.5 and 0.8 SD units represent small, medium and large treatment effects. The effect size for DRSP/EE in Study 305141, which is shown graphically in Figure 2, appears to be about 0.7, with 95% CI ranging from about 0.4 - 0.9, falling in the range of a medium to large effect size, fairly similar to effect sizes calculated from pooled published studies on SSRIs.

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

on January 7, 2004) were utilized in order to compare the treatment effects noted with the SSRIs with that observed for DRSP/EE.

The most reasonable comparison to results obtained with DRSP/EE is with the fluoxetine luteal phase trial, which used the identical outcome measure (the DRSPS, first 21 items), over the same treatment period. On-treatment scores were averaged over the three treatment cycles, as in the DRSP/EE trial. The placebo response is equivalent to that seen in the DRSP/EE trial, as are the study drug responses, both in terms of percent change and actual change from baseline. The recommendation concerning fluoxetine was for an approvable action pending acceptable labeling. Comparative results from this trial and from Study 305141 are shown in Table 68.

The placebo responses for change from baseline were -23 for fluoxetine, vs. -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 study drug responses were -28 to -31 depending on fluoxetine dose, compared to -17 to -34 for Study 305141, depending on treatment sequence. Despite the discrepant placebo response in the DRSP/EE trials, the magnitude of the difference between active study drug and placebo in change from baseline in DRSPS 21 scores was higher in the DRSP/EE than the fluoxetine trial (5 to 8 for fluoxetine, 9.5-14 for DRSP/EE). Even the lower treatment effect seen for fluoxetine was judged to provide adequate evidence of efficacy for the SSRI, supporting a recommendation for approvability.

Table 68 Comparative Results from SSRI Trials and DRSP/EE Trial

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

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

In summary, this study demonstrated a statistically significant advantage of DRSP/EE over placebo in treatment of PMDD symptoms as measured by the first 21 items of the DRSPS. This statistical significance held whether the study was analyzed with treatment assignment collapsed over treatment sequence (as the Applicant did) or whether the treatment arms were compared in each treatment period (as the FDA statistician did). The statistically significant difference appears at the first cycle of treatment, reducing the possibility that unblinding due to drug effects on bleeding patterns may account for the difference. Statistically significant differences were also demonstrated on several relevant secondary endpoints, particularly those concerned with changes in symptoms and function in the week prior to menses. Clinical relevance, proposed by the Applicant to be measured by calculated effect size, appears to be demonstrated with an effect size similar to that seen in a number of published studies of SSRIs used to treat PMDD. In addition, the actual responses, both in terms of actual change and percent change from

baseline in the first 21 items of the DRSPS, are equivalent to or better than those seen for the approved product, fluoxetine, with luteal phase dosing.

The FDA statistician reviewed the two pivotal phase 3 studies and confirmed that Study 305141 showed statistically significant superiority of DRSP/EE to placebo in change from baseline in DRSPS scores (p = 0.02 at TP1, p = 0.001 at TP2). The statistician stated that the drop-out rate, possible carry-over effect and difficulty maintaining the randomization, all pose problems for TP2, but that the results are strongly significant.

However, the statistical reviewer noted that the statistically significant difference between the two treatment arms in Study 305141 at the washout (baseline) cycle preceding TP2 may be an indication that the duration of washout was not sufficient to eliminate the drug carry-over effect. Given the Applicant's use of the washout cycle score as the baseline to which TP2 scores were compared, obtaining the TP2 baseline with 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.

In addition, it is statistically appropriate to analyze only the first phase of a cross-over study design, as randomization is preserved at this point, despite later drop-outs. In this case, a statistically significant result was obtained in TP1.

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

Safety:

There were no deaths and few serious adverse events in this study. Discontinuations due to adverse events were more frequent in the DRSP/EE group, and were most often attributable to adverse events associated with oral contraceptive use, such as menstrual disorders and breast pain, as well as to nausea/vomiting, incoordination and nervousness. The overall frequency of adverse events was higher in the DRSP/EE group (76%) than in the placebo group (61%), and similarly, showed a disproportionate number of menstrual and breast disorders, along with nausea, nervousness and incoordination, occurring in the DRSP/EE group. Special attention was paid to issues of potential concern, including cardiovascular adverse events that might arise as sequelae to hyperkalemia due to DRSP's antimineralocorticoid properties, and VTEs, which are associated with oral contraceptive use. Cardiovascular events (i.e., dizziness) occurred in one subject in each of the exposure arms; in no cases was there any associated potassium level indicating hyperkalemia. There were no VTEs in the trial.

Evaluation of laboratory assessments showed that a small but increased percent of subjects had increases in potassium level while taking DRSP/EE 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. As is recognized for oral contraceptives generally, DRSP/EE had an adverse impact on lipids, primarily affecting triglycerides and total cholesterol, with almost double the percent of DRSP/EE as opposed to placebo subjects shifting from normal baseline values to high values on treatment.

Vital signs data show no worrisome trends.

Overall Risk-Benefit Assessment:

Although the small sample size and marked attrition of subjects prior to completion of both sequences of the cross-over design are limitations of Study 305141, the study does provide adequate evidence of the efficacy of DRSP/EE in treating symptoms of PMDD. A statistically significant advantage to DRSP/EE over placebo on the primary efficacy endpoint, change from baseline in the first 21 items of the DRSPS, was demonstrated. The clinical relevance of this finding was supported by statistically significant findings of efficacy on a number of secondary endpoint measures, particularly those assessing function and global improvement at the time of the luteal phase. In addition, comparisons to similar data obtained in trials of SSRIs for PMDD suggest that the treatment effect of DRSP/EE on PMDD symptomatology is similar to that of these approved products.

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

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

10.3 Line-by-Line Labeling Review

Labeling will be completed during the next review cycle. The following areas of the label specific to the PMDD indication were addressed by the reviewer in this review cycle:

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**APPEARS THIS WAY
ON ORIGINAL**

11 REFERENCES

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-873
Submission Code	N-000
Letter Date	22 Dec 2004
Stamp Date	23 Dec 2004
PDUFA Goal Date	23 Oct 2005 (original)
	23 Jan 2006 (extension)
Reviewer Name	Gerald Willett MD
Review Completion Date	19 Jan 2006
Established Name	Drospirenone 3 mg / Ethinyl estradiol 0.02 mg
(Proposed) Trade Name	YAZ
Therapeutic Class	Hormonal Contraceptive
Applicant	Berlex Laboratories
Priority Designation	S
Formulation	Tablets
Dosing Regimen	One tablet daily (24 days of active followed by 4 days of placebo)
Indication	Contraception
Intended Population	Women at risk for pregnancy

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

An approvable action is recommended by this reviewer for the contraceptive indication of YAZ (24-day active dosing regimen of drospirenone 3 mg/ethinyl estradiol betadex 0.020 mg tablets) under NDA 21-873. Approval is contingent on (1) a determination that the overall safety profile is acceptable (which will require review of supportive safety data submitted within 90 days of the PDUFA goal date and not reviewed during this cycle) and (2) acceptable labeling.

1.2 Recommendation on Postmarketing Actions

The proposed risk management activity and postmarketing safety Study are acceptable.

1.2.1 Risk Management Activity

Product labeling will include, in addition to the standard class warnings for combination oral contraceptives, a Bolded Warning (similar to that for Yasmin) that informs healthcare providers and consumers about the risk of hyperkalemia associated with the use of drospirenone. The Applicant also has committed (letter date 17-Nov-2005) to conducting an educational program for healthcare providers, similar to that conducted for the approved drospirenone containing product, Yasmin. This program should stress the contraindications to its use and additional risks related to its potential for producing clinically significant hyperkalemia. The education program will continue for 3 years after the launch of YAZ in the U.S.

1.2.2 Required Phase 4 Commitments

In addition to the risk management activities described above, the Applicant has committed to a large prospective Phase 4 postmarketing safety Study of YAZ called the International Active Surveillance Study of Women taking Yaz® (INAS Yaz). The amended protocol is found in the Applicant's 18-Aug-2005 submission. This Study is designed in a similar manner to the ongoing European Active Surveillance Study (EURAS) which is assessing vascular adverse events for Yasmin users compared to users of other combination oral contraceptives. These vascular adverse events include deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident. The INAZ Study will have a U.S. component in addition to Europe (⎯ prescribing physicians in the US and approximately ⎯ in Europe). It will compare drospirenone combination oral contraceptives (YAZ and Yasmin) to those which contain other progestagens. The Study will recruit 50,000 women and follow them every 6 months for three years.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Berlex seeks approval of a second drospirenone (DRSP) based combination oral contraceptive, hereafter referred to as YAZ. This contraceptive contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the Applicant's approved product Yasmin (0.02 mg EE per YAZ tablet compared to 0.03 mg EE per Yasmin tablet) and the same amount of drospirenone (3 mg DRSP) per tablet. The product also differs from Yasmin in that the dosing regimen for YAZ consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin.

In the first review cycle for prevention of pregnancy with YAZ (conducted under NDA 21-676), the Applicant received an Approvable Action. The Applicant was asked to demonstrate that there was added clinical benefit for the 24-day active dosing regimen compared to a 21-day active dosing regimen. The approvable letter suggesting how this benefit might be demonstrated is found in the regulatory section of this review.

Subsequent to the Approvable Action, the Applicant filed NDA 21-873 (the present application) for the indication of prevention of pregnancy and the secondary indication of treatment of symptoms of premenstrual dysphoric disorder (PMDD). This review is focused on the portion of NDA 21-873 that consists of the Applicant's Complete Response to the Approvable Action that sought additional data to support the 24-day active dosing regimen of YAZ by demonstrating greater suppression of ovarian function with the 24-day regimen. .This review also includes summaries of the efficacy and safety findings that were included in the original medical officer's review of NDA-21-676 for prevention of pregnancy. The medical review of the PMDD portion of this NDA can be found in a separate review by Lisa Soule MD,

1.3.2 Efficacy

1.3.2.1 Contraceptive Efficacy

The Applicant's protocol for establishing contraceptive efficacy was similar to that for other product submissions in this class. Over ten thousand 28-day cycles were studied in the 24-day YAZ regimen under protocol 303740. More than 200 women completed 13 cycles of use.

The primary efficacy endpoint was the number of "during treatment" pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with Study drug and through 4 days (Applicant's definition) or 14 days (Division of Reproductive and Urologic Products [DRUP] definition) after the last dose of Study drug. The primary efficacy analysis was the Pearl Index, which is the number of "during treatment" pregnancies per 100 women-years of use. The efficacy for the 24-day YAZ regimen, expressed in terms of the Pearl Index is listed in Table A. The values for the Pearl Index in Table A are based on the Medical Officer's

determination of the number of "during treatment" pregnancies and exclude (a) cycles where backup contraception was used, (b) cycles for women over age 35, and (c) cycles for women listed as sexually inactive.

Table A. Efficacy of the 24-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303740)

Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index**	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.41	0.73-2.47

* Calculated by dividing number of days of exposure by "28".
** Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740
Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

1.3.2.2. Additional Contraceptive Efficacy Support from Study 308020 Findings

Study 308020 was a comparative Study of the YAZ 24-day regimen versus Mercilon over 7 cycles. There were no pregnancies in the YAZ 24-day regimen group which led to a Pearl Index of 0.0 with the upper 2-sided 95% confidence limit of 3.41. The Pearl Index for the Mercilon group based on the 1 pregnancy detected during the Study was 0.93 with the upper 2-sided 95% confidence limit of 5.16.

1.3.2.3. Support for 24-Day Active Dosing Regimen Compared to a 21-Day Regimen

The Applicant has shown greater suppression of ovarian activity with the 24-day regimen of 3 mg DRSP/0.02 mg EE compared to a 21-day regimen via Hoogland scoring in protocol 308382. Hoogland scoring assesses ovarian activity in terms of (1) maximal development of ovarian follicles and evidence of ovulation as assessed by sequential ultrasonography and (2) changes in serum concentrations of estradiol and progesterone.

1.3.3 Safety

1.3.3.1 Primary Safety Data for YAZ

1.3.3.1.1 Exposure

The numbers of subjects exposed and number of subjects taking the drug for one year is acceptable. The preliminary estimate (including acne studies and ongoing Study 308021) of the number of 28-day treatment cycles completed is 41,155. The preliminary estimate of the number of women subjects completing 13 cycles of therapy is 2,045.

1.3.3.1.2 Overall Safety Findings

In summary, the safety assessment to date indicates that YAZ has an acceptable safety profile for a highly effective contraceptive product. Additional assessment of the supportive safety data submitted within 90 days of the PDUFA goal date (and not reviewed during this review cycle) is required before a final determination of the safety profile of YAZ can be made.

1.3.3.1.3 Deaths in Clinical trials with 3 mg DRSP / 0.02 mg EE

The following information concerning deaths is current through October 2005 (via safety updates of past and ongoing YAZ studies and a separate medical officer request for this information). There were four deaths reported in the clinical studies of YAZ. Two of these deaths occurred in protocol 303740 (YAZ, 24-day regimen) at the single US Study site. Neither of these deaths was related to Study medication. One of the deaths, secondary to pesticide poisoning, occurred one month following discontinuation of Study drug. The other death, occurring three months after starting Study medication, was secondary to smoke inhalation in a fire. The other two deaths occurred in ongoing Study 308021, which is an open label Study of the 24-day regimen for 13 cycles in 1010 volunteers. One of these deaths was secondary to Goodpasture's syndrome and the other death was secondary to murder. Neither of these deaths is attributable to Study drug.

1.3.3.1.4 Serious Thromboembolic Complications and Other SAEs in the Clinical Studies with 3 mg DRSP / 0.02 mg EE

The finding of two confirmed venous thromboembolic (VTE) adverse events (2 cases of pulmonary emboli in the 21-day active regimen Study 303860) represents a VTE rate of approximately 6.3 per 10,000 women-years for the DRSE/EE product (24 and 21-day active dosing regimens clinical trial data combined) based on a preliminary estimates of 41,155 total treatment cycles or 3,165 women years of exposure).

Medical Officer's Comment

- *This rate is lower than the VTE rate of the approved product Yasmin in the first year of the EURAS Study (approximately 15 cases per 10,000 women-years of use). This rate is also lower than the VTE rate in the Prescription-Event Monitoring (PEM) Study for Yasmin carried out in the UK. The VTE incidence rate in the PEM Study was 13.7 cases per 10,000 women-years. The overall numbers of other drug related serious adverse events (SAEs) in all of the clinical studies is small, and the adverse events are those that are known to be related to the use of combination oral contraceptives.*

1.3.3.1.5 Discontinuations Due to Adverse Events.

In the YAZ 24-day regimen pivotal Study (303740), the adverse events contributing to the greatest number of drug-related discontinuations were headache (14 incidents, 1.3% of subjects) followed by intermenstrual bleeding (0.6%), nausea (0.6%), depression (0.6%), decreased libido (0.6%), dysmenorrhea (0.5%), emotional lability (0.5%) and vomiting (0.5%). All of these events are known side effects of combination oral contraceptives.

Headache was also the most common drug-related adverse event seen in Study 303740 reported by 13.3% of subjects, followed by breast pain (6.9%), vaginal moniliasis (6.5%), leukorrhea (5.6%), and nausea/vomiting (4.6%).

1.3.3.1.6 Safety Lab Findings.

Safety labs were performed in the 24-day regimen protocol (303740). The laboratory analysis from the 24-day regimen Study is sufficient for safety evaluation of 3 mg DRSP / 0.02 mg EE overall. Increased mean levels of lipids (cholesterol and triglycerides) were seen. These findings are comparable to the well-characterized effects of combination oral contraceptives (COCs) on lipids.

Careful potassium monitoring in Study 303740 was performed due to the potential potassium retaining effects of drospirenone. All of the elevated potassium levels identified in the 24-day regimen protocol appeared to represent "pseudohyperkalemia" resulting from hemolysis or transport problems. There was no evidence of true hyperkalemia or any hyperkalemic type symptomatology found at the time of these elevated values. Repeat testing in each case revealed normal values.

The findings of a large Phase 4 cohort claims database Study (the Ingenix Study of Yasmin, see below) and postmarketing reports (AERS) from Yasmin have also provided data that do not show a safety signal regarding an increased the risk of hyperkalemia in women using Yasmin (i.e., 3 mg DRSP /day).

1.3.3.1.7 Vital Signs, Bleeding Patterns

Neither the 24-day nor 21-day regimen showed any significant mean changes in vital signs or body weight. Both the 24-day regimen and the 21-day regimen had acceptable menstrual cycle control data. The levels of pill-associated amenorrhea and intracyclic bleeding were acceptable for both regimens.

1.3.3.2 Supportive Post Marketing Safety Data based on the Approved Product Yasmin

The Applicant has provided data from two large ongoing postmarketing safety surveillance trials that support the safety of the presently marketed DRSP product Yasmin.

1.3.3.2.1 EURAS

The European Active Surveillance Study (EURAS) was initiated for Yasmin in March 2001. This surveillance Study is part of a European effort to perform postmarketing safety on contraceptive formulations with new progestins and/or estrogen. This Study was last updated on 15 June 2005. At that time 59,510 women were enrolled representing 117,153 women-years of observation including 34,310 women-years of exposure to Yasmin. The comparative table (see Table B) shows the thrombotic/thromboembolic adverse event rates for Yasmin, levonorgestrel-based oral contraceptives and "other" oral contraceptives. The results demonstrate that in regard to thrombotic/thromboembolic adverse events. Yasmin has similar rates compared to other combination oral contraceptives.

Table B: EURAS Study: Confirmed Thromboembolic AEs – Number of Events, Incidence, 95% CI

Event Category	Yasmin (34,310 WY)			LNG-containing OCs (32,415 WY)			Other OCs (50,428 WY			Total
	N	Per 10^4 WY	95% CI	N	Per 10^4 WY	95% CI	N	Per 10^4 WY	95% CI	N
All VTE & ATE	28	8.2	5.4 –11.8	25	7.7	5.0-11.4	48	9.5	7.0-12.6	101
All VTE	25	7.3	4.7 - 10.8	20	6.2	3.8-9.5	42	8.3	6.0-11.3	87
Of which PE	7	2.0	0.8 – 4.2	5	1.5	0.5-3.6	8	1.6	0.7-3.1	20
All ATE	3	0.9	0.2 – 2.6	5	1.5	0.5-3.6	6	1.2	0.4-2.6	14
Of which AMI	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	4	0.8	0.2-2.0	6
Of which CVA	3	0.9	0.2 – 2.6	3	0.9	0.2-2.7	2	0.4	0.0-1.4	8
All Fatal VTE/ATE	0	0.0	0.0 – 1.1	2	0.6	0.1-2.2	0	0.0	0.0-0.7	2

VTE = venous thromboembolic event; ATE = arterial thromboembolic event; AMI = acute myocardial infarction; CVA = cerebrovascular accident; WY = women-years
Source: Applicant's 18 Aug 2005 submission (NDA 21-676), page 7 of 13

1.3.3.2.2 Ingenix Study

The US postmarketing surveillance Study (Ingenix Study of United Health Care Patients) was initially designed to monitor adverse events related to hyperkalemia. There has been no signal to suggest that hyperkalemia has been a clinical problem with Yasmin since its approval. The Ingenix Study was later modified to monitor thrombotic and thromboembolic adverse events. The most recent interim analysis of the Ingenix Study (see Table C) shows a similar risk for Yasmin, compared to other oral contraceptives, for thrombotic and thromboembolic adverse events.

Table C: Ingenix Study Results (Confirmed Cases of Thrombotic and Thromboembolic Events)

Thromboembolism Subgroup	Yasmin Cohorts (N=15,767)				Other OC Cohorts (N=31,534)					
	N	PY	IR (1)	95% CI	N	PY	IR	95% CI	RR	95% CI
Pulmonary embolism	5	13,160	0.4	0.1-0.8	7	25,361	0.3	0.1-0.5	1.4	0.3-5.0
Venous thrombosis	12	13,160	0.9	0.5-1.5	22	25,361	0.9	0.6-1.3	1.1	0.5-2.2
Venous thrombosis and pulmonary embolism	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9
Stroke (2)	1	13,160	0.1	0.0-0.4	4	25,361	0.2	0.1-0.4	0.5	0.0-4.9

PY = Person-years; IR= Incidence rate; RR= Rate ratio
1 Incidence rates expressed as events per 1,000 person-years
2 TIA outcomes also counted in stroke.
Source: Applicant's 18 Aug 2005 submission (NDA 21-676), page 7 of 13

1.3.3.2.3 AERS Reporting and ODS Review

An updated report from the Office of Drug Safety (ODS) based on data in the FDA's AERS database through August 31, 2005 has indicated lower reporting rates of thromboembolic adverse events and deaths for Yasmin since their last assessment approximately one year ago (see Table D). It is anticipated that YAZ will have lower spontaneous reporting rates of these adverse events due to the reduced amount of ethinyl estradiol in this product.

Table D: Vascular Adverse Events and Deaths for Yasmin in AERS Reporting Data since U.S. Product Launch.

	Yasmin (May 2001-May 2004)		Yasmin (May 2001-Aug 2005)	
Estimated Total Prescriptions	13,033,000		24,857,000	
Person-Years of Exposure	749,844		1,906,838	
	N	Reporting Rate (per 100,000)	N	Reporting Rate (per 100,000)
All Embolism & Thrombosis	89	11.9	123	6.5
Pulmonary Embolism	43	5.7	53	2.7
Cerebrovascular Events	16	2.1	23	1.2
Myocardial Infarction	Not assessed		2	0.1
All Deaths	6	0.8	6	0.3

Source: ODS reports of August 31, 2004 and November 1, 2005

1.3.4 Dosing Regimen and Administration

The Applicant has provided additional Phase 2 pharmacodynamic data that indicates that the 24-day active dosing regimen is associated with greater ovarian suppression than is the 21-day active dosing regimen. The Applicant's proposed dosing regimen is a 3 mg DRSP/0.02 mg EE tablet daily for 24 days followed by 4 days of placebo tablets.

1.3.5 Drug-Drug Interactions

Like other combination oral contraceptives there are known drug-drug interactions (rifampin, anticonvulsants, antibiotics, atorvastatin and St. John's Wort. In addition there are potential interactions of the drospirenone component of this combination drug with other potassium altering drugs such as ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists and NSAIDs.

In regard to hepatic cytochrome enzymes interaction studies with omeprazole, simvastatin and midazolam have not shown any significant interactions.

1.3.6 Special Populations

Gender - Combination oral contraceptives are intended for the population of women at risk for pregnancy.

Race - A small pharmacokinetic Study was performed by the Applicant comparing Japanese and Caucasian women. This Study showed no differences in these two ethnic populations.

The racial distribution for the 24-day regimen in the pivotal trial 303740 was 87.8% Caucasian; 4.6% Hispanic; 4.3% Black; 1.2% Asian and 2.15 other.

Although there are very few non-Caucasians in these studies, there is no evidence from previous combination oral contraceptive NDAs or from the literature to suspect that the safety or efficacy of estrogen/progestin combination orals differ based on the race of the user.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Berlex seeks approval of a second drospirenone (DRSP) based combination oral contraceptive. This contraceptive (hereafter referred to as YAZ) contains two-thirds the daily level of ethinyl estradiol (EE) that is found in the Applicant's approved product Yasmin (0.02 mg EE per tablet in YAZ compared to 0.03 mg EE per tablet in Yasmin) and the same amount of drospirenone (3 mg DRSP) per tablet.

The product also differs from Yasmin in that the dosing regimen consists of 24 days of active tablets followed by 4 days of placebo tablets compared to 21 days of active tablets followed by 7 days of placebo tablets for Yasmin.

Both of these approaches (lower daily ethinyl estradiol doses and extended pill use past 21-days) have been studied recently for combination oral contraceptives. Lowering the ethinyl estradiol should theoretically provide a better safety margin. This was seen when the dose of ethinyl estradiol was lowered in older combination oral contraceptives (containing ≥ 0.05 mg ethinyl estradiol) to ≤ 0.035 mg of ethinyl estradiol. Proving that lowering ethinyl estradiol to the 0.02 mg range from the 0.03 to 0.035 mg range results in added safety with less thromboembolic disease has been more difficult because it would require huge trials due to the relative rarity of these serious adverse events.

The effort to Study more extended regimens with less placebo use is based on ideas related to additional ovarian suppression which theoretically could translate to less unintended pregnancies. Extended therapies may also have the potential for fewer days of premenstrual symptoms.

National approval of the 21-day regimen of 3 mg DRSP / 0.02 mg EE (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)

2.5 Presubmission Regulatory Activity

In the first review cycle for prevention of pregnancy with YAZ (conducted under NDA 21-676), the Applicant received an Approvable Action. The Applicant was asked to demonstrate that there was added clinical benefit for the 24-day active dosing regimen compared to a 21-day active dosing regimen. The approvable letter suggesting how this benefit might be demonstrated is provided later in this section of this review.

Subsequent to the Approvable Action, the Applicant filed NDA 21-873 (the present application) for the indication of prevention of pregnancy and the secondary indication of treatment of symptoms of premenstrual dysphoric disorder (PMDD. This medical review is focused on the portion of NDA 21-873 that consists of the Applicant's Complete Response to the Approvable Action that sought additional data to support the 24-day active dosing regimen of YAZ. This review also includes summaries of the efficacy and safety findings that were included in the original medical officer's review of NDA-21-676 for prevention of pregnancy. The medical review of the PMDD portion of NDA 21-873 (the current NDA) can be found in a separate review by Lisa Soule MD,

The content of the approvable letter that described the deficiencies of the original submission and the information that would need to be provided to address these deficiencies is provided below:

17 November 2004 Approvable Letter

We have completed our review of this application, and it is approvable. Before the application may be approved, however, it will be necessary for you to (1) demonstrate a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/ethinyl estradiol or (2) propose a 21-day regimen for consideration. This can be accomplished by any of the following:

1. Provide evidence that the proposed 24-day contraceptive dosing regimen provides a clinical benefit over that provided by a 21-day regimen. This evidence could consist of demonstrating fewer "escape ovulations" with the 24-day regimen compared to the 21-day regimen.

Medical Officer's Comment:

- *The Applicant's proposed use of Hoogland scoring which monitors for follicular suppression through multiple determinations (sonography, progesterone and estradiol) is also felt to be acceptable for the comparative Study. Comparative information on the ovarian suppression of both the 24-day and 21-day active dosing regimens was provided during the review of NDA 21-873. These data were a major component of the Applicant's Complete Response to NDA 21-676 that was submitted on June 15, 2005. These data were also submitted to NDA 21-873 by cross reference to NDA 21-676 on July 25, 2005.*

2. Demonstrate that the 24-day regimen is safe and effective for either of the two secondary indications that are presently under investigation, premenstrual dysphoric disorder (PMDD) and acne.

Medical Officer's Comment:

- *The portion of NDA 21-873 that addresses the safety and effectiveness of YAZ for the treatment of PMDD has been reviewed separately by Lisa Soule MD and is not addressed in detail in this review.*

3. Submit an application amendment for the 21-day dosing regimen for the contraceptive indication. The amendment should include acceptable labeling, acceptable financial disclosure information for the investigators who participated in Study 303860, acceptable CMC information regarding final packaging of the 21-day regimen, and a safety update. You can consider a dosing regimen that includes 7 days of placebo tablets instead of 7 tablet–free days.

Regardless of the option chosen, your submission should also include a proposal to conduct an education program for healthcare providers, similar to that conducted for the approved drospirenone containing product, Yasmin (drospirenone and ethinyl estradiol). This program should stress the contraindications to its use and additional risks related to its potential for producing clinically significant hyperkalemia.

Should you continue to pursue approval of the 24-day dosing regimen, your submission should also include a proposal to conduct a large, adequately powered post-marketing surveillance Study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone. This type of Study would not be necessary should you choose to pursue a 21-day dosing regimen.

Labeling remains unresolved. Further discussions regarding this topic will occur in the next review cycle.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Medical Officer's Comment:

- *This reviewer felt that the safety and efficacy data from the original submission was sufficient to warranted approval of the 24 day dosing regimen. Others in the Division sought additional reassurances concerning the 24-day regimen since there would be an additional three days of pill use per cycle. The division has approved two other combination oral contraceptives with extended use past 21-days. Mircette has 5 additional days of ethinyl estradiol use and Seasonale has two additional weeks of use every three cycles.*

- *In the Applicant's complete response of June 15, 2005 for NDA 21-676, the Applicant chose to provide additional evidence of benefit for the 24-day regimen by providing a final Study report for protocol 308382 that indicates more ovarian suppression with the 24-day regimen compared to the 21-day regimen. Although this Study was not powered or designed to show more escape ovulations than in the 21-day dosing regimen, the division has accepted the design of protocol 308382 (greater ovarian suppression based on the Hoagland's criteria [see Section 6.1.4.2.4]) as providing potential supportive evidence for the justification of the 24 day dosing regimen. The Study report for protocol 308382, which*

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was also cross referenced to NDA 21-873 (this NDA), is reviewed in detail by this medical officer in the current medical review.

• *The Applicant has also provided a safety update and commitments in the June 15, 2005 submission to NDA 21-676 (and cross-referenced in this NDA) to (a) apply a risk management program for YAZ similar to Yasmin and (b) conduct a large, adequately powered post-marketing surveillance Study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone.*

2.6 Other Relevant Background Information

National approval of the 21-day regimen of 3 mg DRSP / 0.02 mg EE (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

Medical Officer's Comment:

• *NDA 21-676 is cross referenced from NDA 21-873 for reviews from other disciplines in the following sections.*

3.1 CMC

Chemistry recommends approval from a CMC standpoint. The chemistry review indicated that the Applicant has submitted 36 month stability data during the first cycle review of NDA 21-676 and requested an expiry of 36 months. In the second review cycle, the sponsor submitted 48 months of stability data. Based on the submitted data, an expiry of 48 months can be granted.

3.2 Animal Pharmacology/Toxicology

Pharmacology (Reviewer Krishan Raheja) recommended approval of YAZ during the first review cycle with the following recommendations:

A. Recommendation on Approvability: Pharmacology recommends approval of NDA 21-676 based on previous finding of safety and prior approval of Yasmin (Berlex NDA 21-098), a contraceptive, which contains 3 mg DRSP and 0.03 mg EE. The present proposed formulation, Yaz has the same indication, i.e., contraception and is administered by the same route, but contains only 0.02 mg of EE compared to 0.03 mg in Yasmin.

B. Recommendation for Nonclinical Studies: Preclinical safety is supported by reference to studies that were submitted to support approval of NDA 21-098 for Yasmin. In addition this NDA (NDA 21-676) contains eight pharmacology reports (AW63, B273, B283, A04834, AQ61,

AF46 and AF45), six ADME reports (B206), AV64, B589, B824, A618 and B320) and eight toxicology reports (AG69, B178, B839, AS78, A09791, A09897, A11703 and A11637), which were not previously submitted in NDA 21-098.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data include:

- Original submission for NDA- 21-676 (16 October 2003) and DRUP reviews

- Original submission of NDA 21-873 for the combined indication of prevention of pregnancy and treatment of symptoms of PMDD (secondary indication)

- Complete response submission (June 15, 2005) for NDA 21-676 that is cross=referenced in NDA 21-873 and includes:
    1. Follicular suppression Study 308382
    2. Safety update for 3 mg DRSP / 0.02 mg EE clinical trials not previously reported
    3. Supportive safety updates from Yasmin postmarketing studies

- FDA's Office of Drug Safety review of AERS database reporting rates for oral contraceptives including Yasmin from August 31, 2004 and November 1, 2005

- Additional efficacy and safety information submitted at the request of the Division during the review process. This information was obtained from the Applicant's completed (1) acne studies and (2) comparative Study of YAZ to Mercilon, and an ongoing large European open label safety and efficacy Study for prevention of pregnancy.

4.2 Tables of Clinical Studies

The completed clinical studies for 3 mg DRSP / 0.02 mg EE Tablets (24 or 21 day dosing regimens) are listed in Table 1.

Table 1 Completed Clinical Studies of 3 mg DRSP/0.02 mg EE Tablets (24 or 21 day dosing regimens)

Study No.	Dosing arms/ number of subjects	Description
**Phase 1 and Phase 2 Studies**	
301780	• 3 mg DRSP / 0.02 mg EE 9betadex clathrate); n=18 • 3 mg DRSP / 0.02 mg EE (free steroid) in 18 subjects • 6mg DRSP / 0.04 mg EE (oral microcrystalline suspension) in 18 subjects	Phase 1 Bioavailability Study
300080	• 3 mg DRSP / 0.02 mg EE (betadex clathrate in 18 subjects • 6mg DRSP in 6 subjects • 3 mg DRSP in 6 subjects • 1mg DRSP in 6 subjects	Phase 1 Single dose PK Study in Japan
304326	• 3 mg DRSP / 0.02 mg EE (betadex clathrate in 18 subjects • 6mg DRSP in 6 subjects • 3 mg DRSP in 6 subjects • 1mg DRSP in 6 subjects	Phase 1 Single dose PK Study in Germany
305103	3 mg DRSP / 0.02 mg EE in 48 subjects for 21 days	Phase 1 Multi-dose PK Study
303741	3 mg DRSP in 24 subjects over 14 days	Drug interaction Study with simvastatin
306946	3 mg DRSP in 24 subjects over 9 days	Drug interaction Study with midazolam
305466	3 mg DRSP / 0.02 mg EE in 23 subjects over 2-cycles with 21-day regimen	Phase 2 Ovulation inhibition Study
14588	3 mg DRSP / 0.02 mg EE in 30 subjects over 2-cycles with 21-day regimen	Phase 2 Ovulation inhibition Study
308382	3 mg DRSP / 0.02 mg EE: 24-day regimen (n=52) or 21-day regimen (n=52) for 3 cycles	To Compare the Effects of 24-Day and 21-Day Regimens on Suppression of Ovarian Activity
**Phase 3 Studies with 24-day regimen (YAZ)**	
303740	3 mg DRSP / 0.02 mg EE in 1,027 subjects over 13 cycles with 24-day regimen	Phase 3 Study for safety and efficacy (24-day dosing regimen)
301888	• 3 mg DRSP / 0.02 mg EE in 29 subjects over 7-cycles with 24-day regimen • 0.150mg desogestrel / 0.02 mg EE in 30 subjects over 7 cycles	Comparative Phase 3 Study of plasma lipids, hemostatic variables and carbohydrate metabolism
304049	• 3 mg DRSP / 0.02 mg EE in 231 subjects over 3 cycles • Placebo in 218 subjects over 3 cycles	Phase 3 Premenstrual Dysphoric Disorder (PMDD) Study
305141	• 3 mg DRSP / 0.02 mg EE in 54 subjects • Placebo in 49 subjects	Phase 3 Premenstrual Dysphoric Disorder (PMDD) crossover Study
306820	• 3 mg DRSP / 0.02 mg EE 24-day regimen in 266 subjects for 6 cycles • Placebo in 286 subjects for 6 cycles	Phase 3 Acne Study
306996	• 3 mg DRSP / 0.02 mg EE 24-day regimen in 270 subjects for 6 cycles • Placebo in 268 subjects for 6 cycles	Phase 3 Acne Study
308020	• 3 mg DRSP / 0.02 mg EE 24-day regimen in 229 subjects for 7 cycles • 0.15mg desogestrel / 0.02 mg EE in 220 subjects over 7 cycles	Open comparative Study of YAZ in a 24-day regimen vs Mercilon 2 for 7 cycles in 440 Healthy Female Volunteers" (Draft summary submitted)
**Phase 3 Studies with 21-day regimen**	
14523	• 3 mg DRSP / 0.02 mg EE in 220 subjects over 7 cycles with 21-day regimen • 0.15mg desogestrel / 0.02 mg EE in 221 subjects over 7 cycles	Comparative Phase 3 Study of cycle control for the 21-day regimen
303860	3 mg DRSP / 0.02 mg EE in 516 subjects over 26 cycles	Phase 3 Contraceptive Study (21-day regimen)

__Medical Officer's Comment:__

- *Not listed in Table 1 is Study 308021 which is an on going Phase 3 safety and efficacy Study. The Applicant has provided preliminary safety data from 870 women treated for approximately 11,310 28-day cycles. Safety data for this Study is not complete or fully validated as the Study in ongoing.*

- *Additional safety review and analysis of the acne studies (Studies 306820 and 306996) and of the data from Study 308021 by this reviewer is ongoing.*

4.4 Data Quality and Integrity

Datasets were reviewed to assess accuracy in the summary reports. A biostatistical review of Protocol 308382 (comparative effectiveness of the 21 and 24 day active dosing regimens) was performed and is summarized in Section 6.1.5.

4.5 Compliance with Good Clinical Practices

In regard to __Study protocol 308382__ (comparative effectiveness of the 21 and 24 day active dosing regimens) the Applicant provided the following information:

The Study commenced only after the protocol had been approved by the appropriate ethics committee (EC) and written notification of the approval had been received by Schering AG. The investigator was not to modify or alter this protocol without first obtaining the written agreement of Schering AG. All alterations that were not only of an administrative nature required a formal protocol amendment and were approved by the appropriate EC before the implementation, except where immediate implementation in order to eliminate an imminent hazard to the subject was necessary.

All protocol amendments which were agreed upon were recorded on the standard protocol amendment form provided by Schering AG, and were signed and dated by both the Applicant and the investigator.

The planning and conduct of this clinical Study was subject to national laws. Only when all of the requirements of the appropriate regulatory authority were fulfilled did the Study begin. The Study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) guidelines.

At the discretion of the Study manager, the entire Study could have been cancelled for medical reasons. In addition, Schering Group retained the right to end the Study for medical-scientific or GCP-relevant reasons. In the event of a premature termination, the investigators, EC, and regulatory authorities were to be informed by the Study manager.

4.6 Financial Disclosures

This is not required for the follicular suppression Study 308382. The Applicant properly addressed the financial disclosure requirements in the original review cycle for the 24-day regimen studies.

5 CLINICAL PHARMACOLOGY

In the first review cycle this NDA was found acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

In this review cycle Julie Bullock made the following recommendation:

> "NDA 21-676, YAZ for Oral Contraception is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective."

She also referenced an interaction Study that was discussed in NDA 21-355 (Angeliq):

> "In addition please reference the submission made on March 31, 2005 for NDA 21-355 (Angeliq) which contains a Phase 1 drug-drug interaction Study to evaluate the potential of DRSP to inhibit CYP3A4 using midazolam as a marker substrate for CYP3A4. The review of this Study was completed by Julie Bullock, Pharm. D (Review in DFS). This Study concluded that there is no clinically meaningful interaction between DRSP and midazolam."

6 INTEGRATED REVIEW OF CONTRACEPTIVE EFFICACY

6.1.4 Efficacy Findings

The integrated review of efficacy is composed of two main sections. One is the contraceptive efficacy which was thoroughly evaluated in the first review cycle. A summary of those findings is presented again in this review. The second is the findings of the follicular suppression Study 308382.

6.1.4.1 Contraceptive Efficacy

24-day Dosing Regimen (Primary Efficacy Data)

Protocol 303740 - The Applicant's protocol for establishing contraceptive efficacy is similar to other product submissions in this class. Over ten thousand 28-day cycles were studied in the primary clinical trials for the 24-day YAZ regimen. More than 200 women completed 13 cycles of use.

The primary efficacy endpoint was the number of "during treatment" pregnancies defined as all pregnancies with an estimated date of conception after the onset of treatment with Study drug and through 4 days (Applicant's definition) or 14 days (DRUP's definition) after the last dose of Study drug. The primary efficacy analysis was the Pearl Index, which is the number of "during treatment" pregnancies per 100 women-years of use. The efficacy for the 24-day YAZ regimen,

expressed in terms of the Pearl Index is listed in Table 2. The value for the Pearl Index in Table 2 is based on the Medical Officer's determination of the number of "during treatment" pregnancies and excludes cycles where backup contraception was used, cycles for women over age 35, and cycles for women listed as sexually inactive.

Table 2 Efficacy of the 24-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303740)

Total days of exposure	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index**	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,386	11,050 *	11	12	1.41	0.73-2.47

* Calculated by dividing number of days of exposure by "28".
** Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740
Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

Study 308020 - In Study 308020 (comparative Study with Mercilon) there were 229 subjects in the YAZ 24-day regimen group and 220 subjects in the Mercilon group. This Study lasted for 7 cycles. In the YAZ 24-day regimen, 201 subjects completed the Study medication. In the Mercilon group 196 subjects completed the Study course. There were no pregnancies in the YAZ group which led to a PI / adjusted PI of 0.0 / 0.0 with the upper 2-sided 95% confidence limit of 3.41 for the PI, and that of 3.49 for the adjusted PI. The PI for the Mercilon group based on the 1 pregnancy detected during the Study was 0.93 with the upper 2-sided 95% confidence limit of 5.16. The adjusted PI was similar, 0.93, with the upper 2-sided 95% confidence limit of 5.19.

Medical Officer's Comment:

- *This additional pregnancy prevention data lends added support to the contraceptive efficacy of YAZ, 24-day regimen.*

21 Day dosing regimen (Supportive Efficacy Data)

The following table (Table 3) shows the Pearl Index for the 21-day regimen of YAZ. Protocol 303860 was carried out in a similar fashion to that of protocol 303740.

Table 3 Efficacy of the 21-day YAZ Regimen of 3 mg DRSP / 0.02 mg EE (Protocol 303860)

21-day regimen (protocol 303860)					
Total days of exposure)	Total 28-day cycles of exposure	Total Number Pregnancies		Pearl Index **	2-sided 95% confidence interval
		Applicant's Determination	FDA's Determination		
309,136	11,040	2	3	0.35	0.07-1.04

* = Calculated by dividing number of days of exposure by "28".
** = Pearl Index based on using 12 "during treatment" pregnancies in protocol 303740 and 3 "during treatment" pregnancies in protocol 303860).
Source: Page 11 of Medical Officers Review for YAZ (NDA 21-676), November 16, 2004

Medical Officer's Comment:

- *Differences in the Pearl Index between the two regimens were described in the medical officer review of the original submission. The higher Pearl Index for the 24-day regimen could be partly a result of the different countries involved. Brazil had a disproportionately high number of pregnancies (n=7 with 4 subject failures) in 24-day protocol and Brazil was not part of the 21-day protocol. In addition the 21-day protocol was carried out for 26 months which tends to give better results. The Pearl Index for the 24-day regimen is acceptable. The information regarding ovarian suppression in the following section shows more ovarian suppression with the 24-day regimen compared to the 21-day regimen.*

6.1.4.2 Ovarian Suppression with the 24-Day Regimen Compared to the 21-Day Regimen

The Applicant conducted a Study (protocol 308382) where ovarian suppression was studied using the 24-day regimen compared to the 21-day regimen. The endpoint for this Study was Hoogland scoring in the second and third cycle of use. The third cycle was conducted using a predefined dosing error of 3 missed tablets on days 1 to 3 of that cycle. Hoogland scoring incorporates more parameters than solely measuring serum progesterone and allows additional follicular measurements through frequent sonographic evaluations.

The Applicant showed that the 24-day regimen was statistically better than the 21-day regimen in producing better suppression of ovarian function.

Medical Officer's Comment

- *This reviewer finds the Hoogland scoring to be an acceptable tool for comparing ovarian suppression between the two regimens. The following section focuses on the ovarian suppression efficacy in greater detail.*

6.1.4.2.1 Title of Study:
"Single center, double-blind, randomized Study to compare the effect of SH T 00186 D (3 mg DRSP / 0.02 mg EE) on follicular development in a 24-day regimen versus a 21-day regimen in 100 healthy female volunteers in cycle 2 and after intentional dosing errors in cycle 3"

6.1.4.2.2 Study Objectives:
The aim of this Study was to compare the effects of 3 mg DRSP / 0.02 mg EE in a 24-day regimen versus a 21-day regimen on follicular growth as assess by follicular size, as well as the incidence of ovulation in cycle 2 and after predefined dosing errors in both regimens in cycle 3 (i.e., 3 missed tablets on days 1 to 3 of cycle 3). Ovulation inhibition was assessed by ultrasound monitoring of follicle size and analysis of serum hormone levels (follicle-stimulating hormone [FSH], luteinizing hormone [LH], progesterone, and 17-ß-estradiol [E2]). Ovarian activity was classified according to the Hoogland scoring system as described below in Section 6.1.4.2.4. Safety parameters assessed were adverse events (AEs), laboratory variables, physical and gynecological examinations including cervical smears, vital signs, and body weight.

6.1.4.2.3 Study Design:

The Study was carried out as a single center, double-blind, randomized Study. One hundred subjects were planned with 50 subjects per treatment regimen (24 day regimen or 21 day regimen with 3 mg DRSP / 0.02 mg EE)

In the pretreatment cycle preceding the treatment phase, hormonal contraceptive use was not allowed. The pretreatment cycle started with the first day of bleeding after the screening visit. Follicular growth and ovulation were closely monitored by transvaginal ultrasound (TVU) and serum hormone levels. The subject was admitted to the treatment phase only if the pretreatment cycle was assessed as ovulatory. If ovulation did not occur in the first pretreatment cycle, a second pretreatment cycle could be performed to assess ovulation. If the pretreatment phase was assessed as ovulatory, the subject was randomized to 1 of the 2 treatment groups, in the order of arrival at the center on day 23 of the pretreatment cycle (visit 6).

The treatment phase consisted of 3 cycles, each with 28 treatment days for all subjects. Tablet intake in the first treatment cycle began on the first day of menses. After the third treatment cycle, return to fertility was monitored during a follow-up cycle to demonstrate resumption of ovulation.

Frequent measurements of follicle size and hormone analyses during cycles 2 and 3 were carried out to assess ovarian activity. Since no ovulations took place in the first cycle in previous studies with similar regimens, measurements were only started in treatment cycle 2 in order to assess if a 'stepwise ripening' of follicles had occurred. In treatment cycle 3 the effect of initially 'missed tablets' on ovarian activity was investigated. Return to fertility, i.e., normal ovarian function was examined in a follow-up cycle.

6.1.4.2.4 Primary Efficacy Analyses and Statistical Methods

Efficacy measurements started in cycle 2, since in previous studies with similar regimen, no ovulation took place in the first treatment cycle.

Transvaginal ultrasonography was to be performed at every visit using a transvaginal probe. Print-outs for documentation were to be taken. They were to be labeled with the subject's initials, examination date, and, if necessary, further information, e.g., right / left side of pelvis.
- The diameter of the largest follicle-like structure per ovary (FLS, i.e., follicles or cystic ovarian structures) was to be documented after calculating the average of the transverse and longitudinal diameters.
- The endometrial thickness (double layer) was to be measured.
- The absence or presence of cervical mucus was to be determined.

At visit 6 (admission to treatment) in the pretreatment cycle, the subject was only admitted to the treatment phase if the follicular diameter reached ≥ 15 mm or if ovulation had occurred.

Blood samples (5 mL per sample) for the determination of FSH, LH, progesterone, and E2 were to be taken at the time points displayed in the Study flowcharts. The blood samples were sent to and analyzed by a central laboratory (————————

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The blood samples were to be frozen and collected at the Study center and sent to the central laboratory at the end of the Study. To ensure measurements under identical conditions, all samples were measured in 1 batch at the end of the Study. In addition, in some cases progesterone was measured during the course of the Study in order to verify ovulation, but for this no extra blood sample was needed.

A separate blood sample (5 mL) was taken at each sampling time point for DRSP measurements. This measurement offered an additional means to check the treatment compliance of the subjects (diary cards were another means of checking for compliance). Only for those samples where compliance was doubtful, DRSP levels were assessed through a validated method.

Ovarian activity was classified according to Hoogland (Hoogland and Skouby, 1993) once per cycle for cycles 2 and 3, and for the follow-up cycle based on the results of the transvaginal ultrasonography, the serum progesterone, and E2 analyses. The classification was only possible after hormone measurements were available, i.e., after completion of Study the conduct. The Hoogland scores are defined in the following table (Table 4):

Table 4: Hoogland Scoring System

Score	Activity	Diameter of FLS (mm)	Progesterone* (nmol/L)	E2 (nmol/L)
1	No activity	≤ 10	--	
2	Potential activity	> 10	--	
3	Non-active FLS	> 13	--	≤ 0.1
4	Active FLS	> 13	≤ 5	> 0.1
5	LUF	> 13, persisting	> 5	> 0.1
6	Ovulation	> 13, ruptured	> 5	> 0.1

FLS = Follicle like structure; LUF = Luteinized unruptured follicle
* = Conversion from nmol/L to ng/mL - multiply by 0.3145
Source: Page 38 of 5895, Study report A25848 (NDA 21-676)

All subjects who took at least 1 tablet of Study medication and for whom at least 1 observation after dosing was available were included in the full analysis set (FAS). The other subjects were classified as 'listing only' (LOS). This means, their data are presented in the individual subject data listings but were not be included in any statistical analysis. Subjects were analyzed according to the treatment they actually received.

A volunteer of the FAS was included in the per-protocol-set (PPS) provided she had no major protocol deviation which affected the primary efficacy variable. Major protocol deviations were:
- Follicular diameter < 15 mm at visit 6 in pretreatment cycle
- No ovulation in pretreatment cycle based on hormone profile
- Use of steroid hormone-containing medication during the Study, e.g., contraceptives
- Cycles 2 and / or 3 not performed
- 'Morning after pill' taken during cycles 1, 2 or 3.

The primary efficacy variable was the Hoogland score in cycles 2 and 3.

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For the efficacy variables, analyses of the FAS and the PPS were performed. The analysis of the PPS was regarded as the primary analysis. For the safety variables only the FAS was analyzed. No interim analysis was planned.

6.1.4.2.5 Secondary Efficacy Analyses

Secondary efficacy variables were the serum concentrations of the endogenous hormones progesterone, E2, LH, and FSH, endometrial thickness, and cervical mucus in cycles 2 and 3.

6.1.4.2.6 Subject Disposition

A total of 128 subjects were screened, of whom 23 failed screening. The reasons for screening failure were 'inclusion / exclusion criteria not met' for 16 subjects, withdrawal of consent for 4 subjects, and 'other' reasons for 3 subjects. These 'other' reasons were as follows: irregular cycle with no menses within 8 weeks after visit 1 (subject no. 322), symptoms of dizziness and paresthesia in fingers in precycle (subject no. 332), and 'cycle too long' (subject no. 418).

Randomization numbers were assigned to 105 subjects, among whom 52 subjects were on the 24-day regimen, and 53 subjects on the 21-day regimen. Study treatment was never administered to 1 subject (1.9%, PID 350) on the 21-day regimen for withdrawal of consent. Treatment was administered to 104 subjects, with 52 subjects on each regimen.

Treatment was prematurely discontinued for 5 subjects (4.8%): these were 3 subjects (5.8%) on the 24-day regimen (PIDs 356 and 381 for withdrawal of consent, and PID 324 for an 'other' reason, i.e., unexpected vacation) and 2 subjects (3.8%) on the 21-day regimen (PID 351 for withdrawal of consent, and PID 326 for an AE, i.e., depressive mood. Study course and Study medication were completed by 99 subjects (95.2% of the FAS), with 49 subjects (94.2%) on the 24-day regimen and 50 subjects (96.2%) on the 21-day regimen.

6.1.4.2.7 Datasets Analyzed

All subjects who took at least 1 tablet of Study medication and for whom at least 1 observation after dosing was available were included in the FAS. Subjects not fulfilling these criteria were classified as 'listing only' (LOS). A subject of the FAS was included in the per protocol set (PPS) provided she had no major protocol deviation which affected the primary efficacy variable.

The FAS consisted of 104 subjects, with 52 subjects on the 24-day regimen and 52 subjects on the 21-day regimen.

The PPS comprised 99 subjects, with 49 subjects on the 24-day regimen and 50 subjects on the 21-day regimen.

The LOS comprised 1 subject assigned to the 21-day regimen who never took any Study medication.

6.1.4.2.8 Demographics

The mean height, weight and BMI for subjects in Study 308382 are listed in Table 5.

Table 5: Height, Weight and BMI in Study 308382

	24-Day Regimen		21-Day Regimen	
	Mean	SD	Mean	SD
Derived age [years]	25.6	4.1	25.6	4.4
Height [cm]	170.4	5.8	169.1	6.9
Weight [kg]	64.4	7.3	66.0	9.5
Derived BMI [kg/m2]	22.2	2.5	23.0	2.7

Source: Page 62 of 5895, Study report A25848 (NDA 21-676)

Medical Officer's Comment

- *The mean age and BMI are comparable between the two treatment groups.*

The majority of subjects (98 subjects or 94.2%) in the FAS were Caucasian, i.e., 49 subjects (94.2%) on both treatment regimens, 2 were Asian (24-day regimen), and 1 was Black (21-day regimen). Three subjects had 'other' ethnicity, specified as half Caucasian, half mix (24-day regimen), a quarter Caucasian, half Black, and a quarter Indian (21-day regimen), and half Black, a quarter Asian, and a quarter Red Indian (21-day regimen)

Medical Officer's Comment

- *The imbalance in ethnicity is not considered by this reviewer to be clinically significant in an ovulatory Study such as this one. The Study arms were comparable in other demographic factors (smoking, alcohol consumption, medical history and gynecologic history.) Although more women in the 24-day regimen had recently used oral contraceptives than the 21-day regimen there would be no carry over efficacy effect since all women had to establish ovulation prior to be accepted into the treatment phase.*

6.1.4.2.9 Prior and Concomitant Treatments

Medical Officer's Comment

- *The dataset MED02.xpt was reviewed. There was no evidence of prior or concomitant medication use that would affect the efficacy analysis.*

6.1.4.2.10 Primary Efficacy Results

Hoogland scoring in cycle 2 and cycle 3 were utilized as the primary efficacy endpoints (see Table 6 and Table 7). The two tables list the numbers of subjects in the Hoogland categories at cycle 2 and cycle 3.

Table 6: Results of Hoogland Scoring for Treatment Cycle 2 - FAS

Hoogland Score	24-Day Regimen Total N FAS= 52	21-Day Regimen Total N FAS = 52
1- No activity	45	28
2- Potential activity	5	11
3- Non-active FLS	0	0
4- Active FLS	1	11
5- LUF	0	1
6- Ovulation	0	1
No result	1	0

Source: Page 74 of 5895, Study report A25848 (NDA 21-676)

Table 7: Results of Hoogland Scoring for Treatment Cycle 3

Hoogland Score	24-Day Regimen Total N FAS= 52	21-Day Regimen Total N FAS = 52
1- No activity	27	15
2- Potential activity	8	7
3- Non-active FLS	0	0
4- Active FLS	13	24
5- LUF	0	0
6- Ovulation	1	4
No result	3	2

Source: Page 74 of 5895, Study report A25848 (NDA 21-676)

Medical Officer's Comment

- *In both cycles nearly twice as many subjects are found in the no activity category in the 24-day regimen compared to the 21-day regimen.*

For both the FAS and PPS, the proportion of subjects with Hoogland scores 1 or 2 in cycle 3 (which had 3 intentionally missed tablets at the beginning of the cycle) was higher for the 24-day regimen compared to the 21-day regimen as shown in Table 8)

Table 8: Proportion of Subjects with Hoogland Scores of 1 or 2 in Cycle 3 (FAS)

Treatment	Total No. subjects	No. of Subjects with Scores of 1 or 2	% of Subjects with Scores of 1 or 2	90% CI
24-day	49	35	71.4	[60.81;82.04]
21-day	50	22	44.0	[32.45;55.55]

Source: Page 70 of 5895, Study report A25848 (NDA 21-676)

Medical Officer's Comment

- *This proportional assessment in Cycle 3 was also pre-specified in the original protocol. This table comes from the June 15, 2005 submission and does not represent any recalculation base on conservative evaluation of progesterone levels.*

A proportional odds model was fitted for the Hoogland score as an ordinal response (logarithmic- linear or log-linear model). An estimated odds ratio for having a lower Hoogland score of 1 would mean there was no difference in treatment effects between the 24-day and 21-day regimens. The following table (Table 9) shows the odds ratios for treatment effect in cycles 2 and 3 using the full analysis set (FAS). The table includes the initial efficacy odds ratio submitted by the Applicant in the June 15, 2005 submission in addition to recalculations. The recalculations are based on excluding more subjects based on low progesterone levels in the baseline period. This reviewer felt that more conservative progesterone analysis should be used to identify "ovulatory" subjects. It is noteworthy that the statistical analysis still showed more ovarian suppression with the 24-day regimen compared to the 21-day regimen.

Table 9: Full Analysis – Odds Ratios for Treatment Effect in Cycles 2 and 3 (Includes Recalculations based on excluding Different Levels of Progesterone in Baseline Cycle)

Baseline Determination	Subjects excluded	Cycle	Estimated Odds Ratio	95% CI
Applicant's initial efficacy table		2	6.91	[2.67;20.49]
		3	3.06	[1.44;6.65]
Recalculation with exclusion of progesterone levels not higher than 1.57 ng/mL in baseline cycle	4 from 24-day regimen 4 from 21-day regimen	2	7.56	[2.88; 22.68]
		3	2.68	[1.24; 5.92]
Recalculation with exclusion of progesterone levels not higher than 4.0 ng/mL in baseline cycle	9 from 24-day regimen 9 from 21-day regimen	2	8.47	[3.14; 25.96]
		3	2.65	[1.17; 6.12]

Source: November 1, 2005 Applicant submission (submitted to NDA 21-873 and NDA 21-676)

Medical Officer's Comment

- *In the above table, the odds ratio always exceeds one and the 95% CI does not include one.*

6.1.4.2.11 Secondary Efficacy Results

Of the secondary endpoints examined, the changes in follicle size, LH and cervical mucus appeared supportive of the comparative findings reflected by the Hoogland scoring evidence of greater ovarian suppression with the 24-day regimen compared to the 21-day regimen.

6.1.5 Review of Efficacy by Biostatistics

The conclusion of the ovarian suppression Study by biostatistician Shahla Farr in her review is presented below:

"This study lacked a prospective statistical analysis plan and can only be considered to be descriptive. There is an apparent trend that the 24-day regimen might have some benefit over the 21-day regimen.