Results

Subject Population and Disposition

All of the 24 women (12 per treatment group) who entered the clinical trial completed the study in accordance with the protocol. Twenty-two (22) of the 24 women were Hispanic and ranged from 52 to 76 years of age. The mean (±SD) age and weight were 57 years (±5) and 77 kg (±11) in the placebo group and 62 years (±6) and 70 kg (±7) in the DRSP/E_2 treatment group.

Serum Potassium Concentrations (24-Hr Samples)

Mean, median, minimum, and maximum $AUC_{0\text{-}24\ hr}$ and Cmax values for potassium in each of the treatment groups prior to and at the end of treatment are listed in Table 2.

Table 2. Serum potassium concentrations (based on 24-hr profiles; mEq/L).

	Pretreatment				End of treatment (Day 14)			
	AUC		Cmax		AUC		Cmax	
	Placebo	DRSP	Placebo	DRSP	Placebo	DRSP	Placebo	DRSP
Mean	96.2	89.6	4.6	4.5	91.3	87.4	4.5	4.2
SD	10.2	9.0	0.6	0.6	9.9	11.4	0.5	0.5
Median	97.2	91.5	4.6	4.5	91.3	89.5	4.4	4.3
Min								
Max								

Mean and median AUC and Cmax values for potassium in the DRSP treatment group were lower than those in the placebo group both prior to and on the final day of treatment (Study Day 14). The sponsor's primary statistical analysis for serum potassium – AUC and Cmax values on the final day of treatment, adjusted for pretreatment concentrations – is summarized in Table 3.

Table 3. Comparison of baseline-adjusted serum potassium area under the curve (AUC) and peak concentration (Cmax) on final day of treatment.

Parameter	Adjusted Geometric Mean		D/P Ratio	P-value	90% CL
	Placebo (n=12)	DRSP/E_2 (n=12)			
Cmax (mEq/L)	4.448	4.248	0.955	0.091	0.914, 0.999
AUC (0-24 hr) (mEq•h/L)	88.32	89.16	1.010	0.809	0.944, 1.080

The 90% confidence limits (CL) for the log transformed Cmax and AUC values (0.914, 0.999 and 0.944, 1.080, respectively) fell within the interval of 0.8-1.25, fulfilling the sponsor's protocol definition of bioequivalence for serum potassium in the 2 treatment groups.

Serum Potassium Concentrations (Every Other Day Single Samples)

Mean serum potassium values prior to onset of treatment and every other day during treatment with study drug and the daily change from baseline (based on the difference between each of the daily mean values and the mean of the screen and pretreatment means) are listed in Table 4.

Table 4. Mean daily serum potassium values (mEq/L) prior to and during treatment.

Group	Parameter	Screen	Pre Tx	Treatment Period						
	Study Day:		-2	2	4	6	8	10	12	15
Placebo	Mean	4.42	4.41	4.55	4.45	4.61	4.41	4.52	4.38	4.41
	SD	0.46	0.33	0.55	0.41	0.39	0.37	0.53	0.40	0.39
	Change [A]			0.13	0.03	0.19	-0.01	0.10	-0.04	-0.01
DRSP/E_2	Mean	4.19	4.20	4.47	4.59	4.50	4.49	4.37	4.46	4.46
	SD	0.38	0.27	0.28	0.40	0.32	0.27	0.34	0.24	0.33
	Change [A]			0.27	0.39	0.30	0.29	0.17	0.26	0.26

A: Change from pretreatment = ([daily mean] – [mean of screen and pretreatment means])

Mean daily serum potassium concentrations, assessed every other day during the treatment period, were similar in each of the treatment groups. However, the mean daily changes from the mean pretreatment value were greater in the DRSP/E_2 group. The overall mean change for serum potassium from baseline (mean of the daily mean changes) was 0.06 mEq/L for the placebo group and 0.28 mEq/L for the DRSP/ E_2 group, a difference of 0.22 mEq/L. The p-value for possible treatment effect, based on a repeated measures analysis of these data adjusted for baseline differences, was p=0.0661. Individual serum potassium values ranged from [redacted] in the placebo and DRSP/E_2 treatment groups, respectively.

MEDICAL OFFICER'S ASSESSMENT OF CLINICAL TRIAL NO. 98106

This was a well designed (double blind, randomized, and placebo controlled) clinical trial. The data provided in this abbreviated report were limited almost entirely to serum potassium concentrations; other study findings will be provided later. Based on (1) the sponsor's statement that no subjects were discontinued from the study and (2) the absence of any statement in the report that there were any significant protocol violations, it has been assumed by this reviewer that all subjects adhered to the protocol dosing schedule for both the ACE inhibitor and the blinded study drug (placebo or DRSP/E_2). Collection of blood samples for serum potassium measures throughout the study appeared to be complete.

The sponsor's protocol-defined analysis of the 24-hour serum potassium data based on AUC and Cmax values did not reveal any effect of DRSP/E_2 treatment on serum potassium concentrations. However, a supplemental analysis, based on serum potassium concentrations in blood samples obtained once a day in the morning, approximately every other day during the treatment period, suggested a possible treatment effect (p=0.0661 for treatment effect). The effect of DRSP/E_2 treatment on serum potassium, however, was small. The overall mean change for serum potassium from baseline (mean of the daily mean changes) was 0.06 mEq/L for the placebo group and 0.28 mEq/L for the DRSP/ E_2 group, a difference of 0.22 mEq/L. This increase in serum potassium is similar to that which has been reported in hypertensive patients treated with ACE inhibitors (see labeling for ACE inhibitors).

CLINICAL PROTOCOL NO. 303063

Study Title

"Open-label study to assess the effects of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days."

Study Objectives

The primary objectives of this study were (1) to evaluate the effect of treatment with DRSP on serum potassium in volunteers with mild or moderate renal insufficiency in order to assess the risk of

hyperkalemia in renally impaired patients and (2) to evaluate the pharmacokinetics of DRSP in renally impaired patients.

Study Design and Treatment

This was a Phase I, single center, open label, 3-group, parallel study. Subjects who met the entry criteria were tentatively assigned to 1 of 3 renal function groups based on their estimated creatinine clearance as initially determined by the Cockcroft-Gault formula (see Table 5).

Table 5. Classification of renal function based on 24-hr creatinine clearance.

Group	Description of renal function	Creatinine Clearance
1	Normal	> 80 mL/min
2	Mild impairment	> 50-80 mL/min
3	Moderate impairment	30-50 mL/min

Prior to initiation of treatment with study drug, an actual 24-hour urinary creatinine clearance measurement was to be performed. The value obtained by this latter procedure was to be used for final group assignments. Approximately 10 subjects were to be enrolled into each of the 3 groups. All subjects were to receive 3 mg of DRSP once daily in the evening for 14 consecutive days. Subjects were also instructed to avoid foods with a high potassium content.

Study Population.

Inclusion Criteria Included

1. Women, 18-75 years of age, with a body mass index of 18-29;
2. Relatively good health other than renal insufficiency; and
3. Creatinine clearance ≥ 30 mL/min.

Exclusion Criteria Included

1. Preexisting or current disease that could interfere with the objectives of the study;
2. Conditions that are generally considered to be contraindications (absolute or relative) to the use of hormonal contraceptives including current smoking, migraine accompanied by disturbance in sensory perception or locomotion, Pap smear showing evidence of epithelial cell abnormality of > II (grading scale 1-V), vaginal bleeding of unknown etiology, and history of thromboembolic disorders or thrombophebitis;
3. History, suspicion or previous diagnosis of cancer of any type as well as benign tumors of liver and pituitary;
4. Severe metabolic disturbances (e.g., insulin-dependent diabetes, severe lipid disturbances);
5. Severe disease or condition within the 4 weeks prior to study drug administration that could have affected serum potassium such as dialysis, hematological disorders or traumatic tissue damage;
6. Serum potassium concentration > 4.8 mmol/L;
7. Previous diagnosis of cancer other than minor skin lesions successfully treated;
8. Subjects who received (a) within 8 weeks prior to first administration of study drug any medication or substance that opposed the study objectives, any drug known to induce or inhibit liver enzymes, any broad-spectrum antibiotic, or any investigational drug or (b) within 6 weeks prior to first administration of study drug any sex hormone; and
9. Subjects who took any diuretics, non steroidal antiphlogistics, or digoxin within 8 weeks before study drug administration that could have had an impact on potassium balance except for

treatment with ACE inhibitors, angiotensin II receptor antagonists, or beta-blockers if the serum potassium concentration was ≤ 4.4 mmol/L and had been stable for at least 3 months.

Study Procedures and Study Conduct

The study was conducted primarily on an outpatient basis at a single center in France. Subjects were also studied for two 24-hour periods in an inpatient facility prior to treatment with DRSP and on the final day of treatment.

Pharmacodynamic Assessments

Serum Potassium Assessments. Blood samples for serum potassium levels were obtained in the morning prior to, during, and following treatment with DRSP (See Table 6 for the blood-sampling schedule). The effect of DRSP on serum potassium in each subjects was assessed primarily in terms of the change in potassium levels defined as the difference between the end-of-treatment mean value (mean of Days 13, 14, and 15) and the pretreatment mean value (mean of Pretreatment Days -2 and -1 and the sample obtained prior to dosing on Treatment Day 1). Blood samples for serum potassium assessments were also obtained approximately every other day during the treatment period for safety monitoring. Potassium concentrations were determined using an ion selective electrode method. The normal range for serum potassium was 3.8-5.2 mmol/L.

Table 6. Blood sampling schedule for assessment of serum potassium concentrations.[A]

	Pre-Tx (Day)		Treatment Period (Day)								Follow-up Period (Day)		
Purpose of Sample	-2	-1	1	3	5	7	9	11	13	14	15	16	21
Safety				X	X	X	X	X	X	X		X	X
Primary PD Endpoint [B]	X	X	X [C]						X	X	X		

[A] Samples were obtained in the morning approximately 12 hours after dosing with DRSP.
[B] Primary pharmacodynamic (PD) endpoint.
[C] Obtained prior to the first dose of DRSP.

Acid-base and sodium assessments. Blood samples for the measurement of sodium and peripheral venous blood gas analysis were obtained prior to treatment (baseline assessment) and 12 hours after the final dose of DRSP on Day 15.

Pharmacokinetic Assessments

Blood samples for measurement of serum concentrations of DRSP and calculation of pharmacokinetic parameters were collected immediately prior to the first dose of DRSP (single sample), immediately prior to the final dose of DRSP on Treatment Day 14, and at 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after the final dose of DRSP.

General Safety Assessments

General safety was assessed by pre- and post treatment measurements of standard serum chemistries, complete blood counts, urinalysis, and reported adverse events.

Results

Subject Population and Disposition

Thirty-eight women were screened and 28 subsequently were enrolled into the study. Based on the results of their pretreatment 24-hr creatinine clearance, subjects were assigned to Group 1 (n=11), Group 2 (n=10) or Group 3 (n=7). No subject terminated prematurely because of an adverse event and all completed the study. All subjects were Caucasian and ranged from 30 to 65 years of age.

Mean (±SD) ages were 41.2 yr. (±11.3) in Group 1, 47.0 yr. (±9.9) in Group 2 and 49.1 (±8.0) in Group 3. Mean values for height and weight were similar across the 3 groups. Five of the subjects had undergone a kidney transplant – one in each of Groups 1 and 2 and 3 in Group 3. Twenty-four (24)-hour creatinine clearance values in the 3 Groups are summarized in Table 7.

Table 7. 24-hour creatinine clearance at baseline.

		24-hr creatinine clearance (ml/min)	
Group	**No. of Subjects**	**Mean**	**Range**
1	11	122.4	
2	10	66.9	
3	7	43.0	

Seven subjects also took medications (ACE inhibitor alone [1 subject], ACE inhibitor plus beta-blocker [2 subjects], or beta-blocker alone [4 subjects]) that, according to the sponsor, had the potential to affect serum potassium levels.

Protocol Violations

There were no protocol violations concerning administration of study drug or the use of prohibited concomitant medications. Six subjects had potassium values at screening that slightly exceeded the upper limit for inclusion into the study. Two subjects, both in Group 3, each had a single potassium value that was ≥ 5.5 mmol/L on one occasion, a value that should have necessitated their withdrawal from the study according to the protocol. None of these violations should impact upon the interpretation of the study findings.

Pharmacodynamic Findings

Observed Serum Potassium Concentrations. Mean pretreatment values, mean end-of-treatment values (Study Days 13-15), and mean values for change from pretreatment to the end of treatment for serum potassium in each of the Groups are listed in Table 8.

Table 8. Pretreatment and end-of-treatment serum potassium concentrations.

		Serum Potassium (mmol/L)		
		Group 1	**Group 2**	**Group 3**
Pretreatment [A]				
	Mean (SD)	3.95 (0.27)	4.45 (0.26)	4.57 (0.26)
End of Treatment [B]				
	Mean (SD)	3.85 (0.24)	4.25 (0.30)	4.47 (0.45)
Change (End-of-Tx – PreTx)				
	Mean	-0.10 (0.22)	-0.20 (0.23)	-0.10 (0.32)
	Max change [C]	0.33	0.23	0.33

[A] Mean of values obtained on Pretreatment Days -2 and -1 and Treatment Day 1 prior to first dosing.
[B] Mean of values obtained on Study Days 13, 14, and 15.
[C] Maximum change for any subject in respective Group.

The mean pretreatment and end-of-treatment serum potassium concentrations were inversely related to renal function. The lowest mean serum potassium values, both before and at the end-of-treatment

with DRSP, were observed in Group 1 while the highest values were observed in Group 3. In each Group, the mean of the end-of-treatment potassium values was numerically lower than the mean of the pretreatment values (range of mean differences: -0.10 to -0.20). The maximum end-of-treatment serum potassium increase, relative to baseline, that was observed in any subject was 0.33 mmol/L. Table 9 lists the end-of treatment mean serum potassium concentration (mean of Study Days 13, 14, and 15) and the end-of-treatment change from baseline for each of the 28 subjects. Five of the 28 subjects had end-of-treatment serum potassium increases that were greater than 0.1 mmol/L. Four of these 5 subjects were also being treated with a beta-blocker and/or an ACE inhibitor.

Table 9. Mean end of treatment serum potassium (mmol/L) and change from baseline

Group 1			Group 2			Group 3		
Subject	End of Tx	Change	Subject	End of Tx	Change	Subject	End of Tx	Change
1	4.10	- 0.13	9	3.93	0.03	12	4.00	- 0.40
2	4.03	0.33	10	4.10	- 0.37	21 [B]	5.10	0.23
3	3.97	- 0.20	14	4.03	- 0.37	22	4.53	- 0.27
4	3.37	- 0.23	15	3.97	- 0.33	24 [C]	4.67	0.33
5	3.80	0.10	16	4.50	- 0.20	25	4.17	- 0.43
6	3.90	- 0.20	17	4.37	- 0.30	26 [A]	4.90	0.10
7	3.60	- 0.27	18	4.63	- 0.20	27 [A]	3.93	- 0.27
8	3.83	- 0.13	19	3.90	- 0.53			
11	4.10	- 0.40	23 [B]	4.40	0.00			
13	3.60	- 0.20	28 [A]	4.67	0.23			
20 [A]	4.03	0.20						

[A] Subject also being treated with a beta-blocker;
[B] Subject also being treated with a beta-blocker and an ACE inhibitor;
[C] Subject also being treated with an ACE inhibitor.

Review of the individual every other day serum potassium values throughout the entire treatment period (Table 52, pg 172 of Sponsor's Final Report) showed that 5 of the 28 subjects had one or more values greater than 5 mmol/L during or within 48 hours of final dosing with DRSP. Two of the 5 subjects were in Group 2 (mild renal impairment) and the other 3 were in Group 3 (moderate renal impairment). All serum potassium values > 5.0 mmol/L were ≤ 5.2 mmol/L with one exception, a single value of 5.5 mmol/L in a Group 3 subject.

Statistical Modeling. The Sponsor, in accordance with the Protocol, also investigated the relationship between renal function and serum potassium by multiple linear regression based on the data obtained from the present study. The sponsor stated in the Protocol that age, serum potassium at baseline, and creatinine clearance would likely be used in the model. The sponsor, based on the data obtained in this study, decided that the most appropriate model to describe potassium levels during treatment included terms for baseline potassium and selected potassium sparing co-medications (e.g., ACE inhibitors). Pretreatment creatinine clearance was eliminated from the model since it correlated with pretreatment potassium values. Based on this revised model, the Sponsor concluded that there was a possibility that subjects with impaired renal function and upper normal baseline serum potassium could develop hyperkalemia if treated with both DRSP and a potassium-sparing co-medication (e.g., an ACE inhibitor).

Acid-Base and Sodium Assessments. Mean (SD) values for pH, pCO_2, bicarbonate, and base excess/deficit in each of the Groups are listed in Table 10. Treatment with DRSP appeared to have a small effect on acid base balance that was most apparent in the subjects with renal insufficiency. The

means of the end-of-treatment pH values in Groups 2 and 3 were slightly below the lower limit of the normal reference range and were each 0.05 units lower than the mean of their respective pretreatment values. The means of the end-of-treatment base excess/deficit values in Group 2 (-2.8 mmol/L) and Group 3 (-5.4 mmol/L) were also below the lower limit of the normal reference range (-2.0 mmol/L).

Table 10. Mean (SD) acid-base parameters based on venous blood gas analysis.

		Group 1	Group 2	Group 3
pH (nl range: 7.36-7.42)				
	Baseline	7.35 (0.04)	7.37 (0.03)	7.37 (0.04)
	End of Tx	7.37 (0.03)	7.32 (0.03)	7.32 (0.07)
	Change	+ 0.02 (0.06)	– 0.05 (0.04)	– 0.05 (0.03)
pCO_2 (nl range: 37-50 mm Hg)				
	Baseline	48.3 (4.9)	41.2 (6.1)	40.0 (7.7)
	End of Tx	41.5 (3.2)	45.2 (5.3)	39.6 (6.6)
HCO_3^- (nl range: 22-30 mmol/L)				
	Baseline	26.3 (2.5)	23.8 (4.1)	23.1 (4.2)
	End of Tx	23.7 (1.4)	23.0 (2.5)	20.4 (4.1)
Base excess/deficit (nl range: -2 to +3 mmol/L)				
	Baseline	1.0 (2.7)	– 1.2 (4.4)	– 1.8 (4.4)
	End of Tx	–1.2 (1.6)	– 2.8 (2.7)	– 5.4 (4.9)
	Change	– 2.2 (3.8)	– 1.6 (3.7)	– 3.6 (3.2)

Mean serum sodium concentrations at baseline and at the end-of-treatment and the mean of the changes from baseline in each of the 3 Groups are listed in Table 11. The decreases in sodium concentrations were most pronounced in the renally impaired subjects (Groups 2 and 3). The mean sodium concentration in Group 3 at the end-of-treatment (133 mmol/L) was slightly below the lower limit of the normal reference range (135-148 mmol/L).

Table 11. Mean (SD) serum sodium concentrations and change from baseline. [A]

	Group 1	Group 2	Group 3
Baseline	139.5 (2.3)	143.8 (2.5)	141.9 (4.4)
End of Tx	138.0 (2.7)	138.7 (2.1)	133.3 (5.8)
Change	-1.5 (3.0)	-5.1 (3.5)	-8.6 (4.2)

[A] nl range: 135-148 mmol/L

Pharmacokinetic Findings

The geométric mean values for the pharmacokinetic parameters of Cmax, half-life ($T_{1/2}$), $AUC_{0\text{-}24\ hr}$ and oral clearance at steady state (CLss/F) for DRSP in each of the 3 renal function groups are listed in Table 12. The clearance of DRSP was reduced and the values for Cmax, $T_{1/2}$ and $AUC_{0\text{-}24\ hr}$ were increased in Group 3 (moderate renal insufficiency) relative to those in the other 2 groups. Additional information about the pharmacokinetic findings is provided in the biopharmaceutical review for this clinical report.

Table 12. Pharmacokinetic parameters (geometric mean and CV) for DRSP by renal function group

Parameter	Group 1 (n=11)	Group 2 (N=10)	Group 3 (n=7)
Cmax [ng/mL]	35.8 (44%)	39.6 (31%)	42.4 (43%)
$T_{1/2}$ [hr]	33.6 (33%)	32.4 (28%)	42.8 (23%)
$AUC_{0-24\ hr}$ [ng•h/mL]	549 (31%)	573 (19%)	751 (47%)
CLss/F [ml/min]	91.0 (31%)	87.3 (19%)	66.6 (47%)

General Safety Findings

No subject terminated from the study because of an adverse, and all subjects completed the 14-day treatment period. No serious adverse events were reported. A total of 10 adverse events were reported in 7 (25%) of the 28 subjects during the treatment phase of the study. Four of the 10 adverse events, reported in a total of 3 subjects, were assessed as possibly related to treatment with the study drug. These possibly related adverse events were headache and tachycardia (both of moderate severity in one subject), and one instance each of abdominal pain (mild severity) and arthralgia (moderate severity). All reported adverse events appeared to have resolved spontaneously, without interruption of study drug or medical intervention.

MEDICAL OFFICER'S ASSESSMENT OF STUDY No. 303063

In this study, treatment with 3 mg of DRSP per day for 14 consecutive days had little apparent effect on serum potassium concentrations in subjects with normal renal function and those with mild and moderate renal impairment. The mean end-of-treatment serum potassium concentrations (mean of Study Days 13, 14 and 15) in each of the 3 renal function groups were not significantly different than their respective pretreatment mean values. Only 5 of the 28 subjects had end-of-treatment serum potassium increases that were greater than 0.1 mmol/L (2 of 11 subjects in Group 1; 1 of 10 subjects in Group 2, and 2 of 7 subjects in Group 3). Four of these 5 subjects were also being treated with a beta-blocker and/or an ACE inhibitor. The maximum end-of-treatment serum potassium increase, relative to baseline, that was observed in any subject was 0.33 mmol/L. Five of the 28 subjects had one or more potassium values greater than 5.0 mmol/L during or within 48 hours of final dosing with DRSP. Two of the 5 subjects were in Group 2 (mild renal impairment) and the other 3 were in Group 3 (moderate renal impairment). None of the subjects, including those with mild or moderately impaired renal function, had a potassium concentration greater than 5.5 mmol/L.

In this study, treatment with DRSP appeared to have a small effect on acid-base and sodium homeostasis. This effect was most evident in the subjects with the greatest degree of renal impairment. In Group 3 (subjects with moderate renal impairment), mean values for pH (7.32), base excess/deficit (-5.4 mmol/L) and sodium (133 mmol/L) at the end of treatment were all slightly below the lower limit of the normal reference range. In contrast, all end-of-treatment means for these parameters were within normal limits in Group 1 (subjects with normal renal function).

Although treatment with DRSP in this study had little apparent effect on serum potassium concentrations, one must view these findings with some degree of caution for several reasons:

- This was a small study, enrolling only 17 subjects with impaired renal function. Elevated serum potassium (greater than 5.7 mEq/L) has been observed in only approximately 1% of hypertensive patients treated with an ACE inhibitor in clinical trials (see labeling for ACE inhibitors). If the effect of DRSP on serum potassium levels in renally impaired subjects is similar to the of an ACE inhibitors on serum potassium in hypertensive patients, a study involving only 17 subjects would

not be adequately powered to assess the risk of developing hyperkalemia during treatment with DRSP in renally impaired patients.

- Subjects were maintained on a low potassium diet.
- The mathematical model developed by the sponsor for predicting the possible effects of treatment with DRSP on serum potassium levels indicated that there was a possibility that subjects with impaired renal function and upper normal baseline serum potassium levels could develop hyperkalemia if treated with both DRSP and a potassium-sparing co-medication (e.g., an ACE inhibitor).

This reviewer recommends that Yasmin not be used in women with renal insufficiency because of (1) the potential risk of hyperkalemia in this population and (2) the lack of a medical need for an oral contraceptive containing a progestin with antimineralocorticoid activity in this population. This restriction could be reassessed if additional relevant medical information becomes available.

SAFETY UPDATE; REPORTING PERIOD: JANUARY 16, 2000 TO MARCH 17, 2000 (Submission Date: May 4, 2000)

The Approvable Letter of March 17, 2000 requested that Berlex update their NDA by submitting all safety information that they had at that time. In response to this request, Berlex submitted a brief Safety Update for the reporting period of January 16, 2000 through March 17, 2000. The reporting dates of this Safety Update were based on the cut-off date for inclusion of data into the previous Safety Update Report (submitted on February 3, 2000) and the date of the Approvable Letter. In the introduction to this Safety Update, Berlex states the following:

> "As with the previous Safety Update, this report refers only to new data obtained during the reporting period. These additional data are relatively few; therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died, subjects who failed to complete a clinical study due to an AE and the results of one nonclinical trial are described..."
>
> "It was concluded that there is no new safety information learned about DRSP 3 mg and EE 0.030 mg Tablets that may reasonably affect the statement of Contraindications, Warnings and Adverse Reactions in the DRAFT Labeling [of February 29, 2000]. The nonclinical report completed during the reporting period contains safety information about DRSP 3 mg and EE 0.030 mg Tablets that affect Item 10, Carcinogenesis, of the Precautions section in the DRAFT labeling...."

Additional clinical information was requested of Berlex on June 8 to clarify some of the information in the Safety Update of May 4, 2000. A reply to this request was received by the FDA on June 16, 2000.

Clinical information contained in the Safety Update of May 4, 2000 are based primarily on final data from Protocol 97036 entitled "A Multicenter, Double-Blind, Randomized, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy of a Monophasic Oral Contraception Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 30 µg, in the Treatment of Premenstrual Syndrome (PMS)" that has been conducted [redacted] (Division of Neuropharmacologic Drug Products).

Enrollment

Study 97036. Two hundred sixty one (261) subjects were randomized. One hundred five (105) completed the 6 cycle study. One hundred thirty (130) were treated with DRSP/EE and 131 were treated with placebo.

Other studies. No information provided.

Serious adverse events

Study 97036. Five subjects experienced 7 serious adverse events. Two of these subjects received placebo and 3 received DRSP/EE. The 3 subjects who experienced serious adverse events were: Subject No. 03001 (pulmonary tuberculosis); Subject No. 07038 (migraine headaches and recurrent Bell's Palsy), and Subject 24004 (basal cell carcinoma of the nose; incorrectly listed as Subject No. 24014 per Sponsor's FAX of June 16, 2000). The drug relationship for the serious adverse event(s) in each of these subjects was classified as "not related." Subject Nos. 07038 and 24004 completed the study.

Other studies. No serious or potentially serious adverse events were reported in any of the other studies that were ongoing during the reporting interval.

Unusually high frequency of a less serious event

The sponsor stated (without providing any actual data or tabulations) that "there was not an unusually high frequency of a less serious event in any of the studies that were ongoing during the reporting interval."

Subjects who died

No subjects died in the studies that were ongoing during the reporting period.

Subjects who discontinued due to an adverse event

Study 97036. Twenty-seven (27) subjects discontinued the study due to an adverse event (20 in the DRSP/EE group and 7 in the placebo group). Adverse events leading to discontinuation in 3 of the 20 subjects in the DRSP/EE groups were assessed as not being related to treatment with study drug. Adverse events leading to discontinuation and felt to be possibly or probably related to treatment with DRSP/EE and the number of occurrences of each were nausea or nausea and vomiting (n=5), headache (n=4), breast tenderness (n=3), and one case each of menorrhagia, migraine, vertigo, palpitations, depression, decreased libido, hypertension, and abdominal pain.

Other studies. There were no discontinuations due to an adverse event during the reporting period.

Countries in which the drug has been approved for marketing during the reporting period

The drug was approved for marketing in the Netherlands on March 7, 2000.

New applications submitted

No new applications for marketing were submitted.

Reports from Foreign Regulatory Agencies

The drug has not been marketed to date; there are no reports related to adverse safety experiences from foreign regulatory authorities.

Reports from literature

The Sponsor states that a review of the literature disclosed no new information that would impact on safety labeling.

Nonclinical reports

See toxicology review.

MEDICAL OFFICER'S ASSESSMENT OF SAFETY UPDATE OF MAY 4, 2000

This brief safety update suffered from a lack of detail in some area (e.g., listing of adverse events leading to study discontinuation did not include severity, outcome, start and stop dates) and the sponsor also did not provide any summary tabulations. However, the adverse events reported as possibly or probably related to treatment with DRSP were not unexpected in women being treated with a combination medication containing a progestin and estrogen. The frequency of these adverse events, relative to one another, also was not unusual. The basis for the 3 to 1 ratio of discontinuations in the DRSP/EE group relative to that in the placebo group for drug-related adverse events (20 in the DRSP/EE group and 7 in the placebo group) is not apparent. The sponsor could not provide an

explanation other than that the adverse events leading to study discontinuation were common in women receiving a combination oral contraceptive. In summary, no worrisome adverse events or patterns of adverse events were observed in these limited data.

MEDICAL OFFICER'S RECOMMENDATIONS

1. Based on the findings in Study No. 98106, the effect of DRSP/E_2 on serum potassium concentrations is not of sufficient magnitude to recommend that Yasmin not be used in women with normal renal function who are also being treated with an ACE inhibitor. Although the Sponsor has not provided data concerning the interaction of DRSP with other drugs (e.g., potassium sparing diuretics) that may also increase serum potassium levels in women with normal renal function, it is reasonable to assume that the findings would be similar to those in Study No. 98106.

   Since Yasmin will be the first approved hormonal contraceptive containing a progestin with antimineralocorticoid activity, physicians need to be informed of the potential interaction of Yasmin with other drugs that also have the potential to increase serum potassium levels.

   a. It is recommended that the labeling for Yasmin include information that informs the physician that Yasmin has the potential to increase serum potassium levels. The following, or similar wording, should be included in the Yasmin label in the section on Drug Interactions:

      "Interactions of Drospirenone

      Interactions With Drugs That Have The Potential To Increase Serum Potassium

      There is a potential for hyperkalemia to develop in women taking Yasmin with other drugs that may increase serum potassium levels. Such drugs include ACE inhibitors, NSAIDS, potassium sparing diuretics, heparin, and aldosterone antagonists."

   b. It is recommended that the description of the findings from the ACE inhibitor Study (Protocol No. 98106) in the draft label for Yasmin submitted by Berlex on May 9, 2000 be modified and include the observation that there was an increase in serum potassium in the DRSP/E_2 treatment group in the samples obtained every other day during the treatment period. A statement such as the following should be added to the description of the outcome of this study in the Yasmin label:

      "Potassium levels were obtained every other day during the 2-week treatment period in all subjects. Mean serum potassium levels in the DRSP/E_2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. No patient in the DRSP/E_2 group had an absolute potassium level higher than 5.2 mEq/L."

2. It is recommended that Yasmin not be approved for use in women with renal insufficiency based on the findings from Study No. 303063 (see Medical Officer's assessment on pages 11 and 12 of this review) and the known clinical pharmacology of DRSP. This restriction could be reassessed at a later time, if additional relevant medical information becomes available.

   A bolded warning such as the following should be included in the label for Yasmin.

   "**Yasmin is contraindicated in patients with renal insufficiency. Yasmin contains the progestin drospirenone, which has antimineralocorticoid activity. Potential risks in renally impaired patients include hyperkalemia, hyponatremia, and metabolic acidosis.**"

3. There are no further safety issues regarding NDA 21-098 (other than those addressed in the Approvable Letter of March 17, 2000) based on (a) the information provided in the Safety Update for the period January 16, 2000 to March 17, 2000 and (b) the pharmacodynamic and other safety data provided in the abbreviated report for serum potassium levels in Study No. 98106 and the final report for Study No. 303063. Issues raised in the Approvable Letter of March 17, 2000 will be addressed in the revised labeling as described in Items No. 1 and 2 above.

/S/

Scott E. Monroe, MD
Medical Officer, DRUDP

Date

/S/

Marianne Mann, MD
Deputy Director, DRUDP

Date

Cc: NDA 21-098
HFD-580
S. Allen, M. Mann, D Hixon, S. Monroe

APPEARS THIS WAY
ON ORIGINAL

FEB 23 2000

Medical Officer's Original Summary
NDA 21-098

Date of Submission	May 14, 1999
Date Received	May 17, 1999
Date Review Completed	February 15, 2000
Applicant	Berlex Laboratories, Inc.
Drug (generic name)	Ethinyl Estradiol and Drosperinone
Proposed Trade Name	**Yasmin™**
Pharmacologic Category	Progestin and estrogen combination
Proposed Clinical Indication	Prevention of pregnancy
Dosage and route of Administration	3 mg drospirenone and 30 µg ethinyl estradiol given as a daily oral tablet for 21 days followed by a 7-day drug-free interval
Manufacturing Control Data	See Chemistry Review
Pharmacologic Data	See Pharmacology Review
Biopharmaceutics Data	See Biopharmaceutics Review
Reviewer	Dena R. Hixon, MD, FACOG Medical Officer, DRUDP

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TABLE OF CONTENTS

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1.0 RESUME

Two pivotal efficacy and safety studies and 33 supportive clinical trials support this NDA for the prevention of pregnancy in women who elect to use a combined oral contraceptive method. Studies included in this review provide information on a total of 3,016 subjects exposed to treatment with any dose of drospirenone (DRSP). 2,776 subjects were exposed to 3 mg DRSP/30 µg ethinyl estradiol (EE) (Yasmin™). 1,913 subjects completed at least 13 cycles of use. The total number of cycles of Yasmin™ use exceeds 30,556, and 849 additional cycles with any dose of DRSP.

European Study 92052 (Pivotal Report A151) was a multi-center, open-label, parallel group, Phase III study in which 887 reproductive aged women were randomized and received either Yasmin™ (n=442) or 0.15 mg Desogestrel + 30 µg EE (Marvelon®, marketed in the U.S. as Desogen®) (n=445) for 26 cycles. 310 women completed 26 cycles of Yasmin™. 73 % of participants were on oral contraceptives at baseline. 98% of participants were Caucasian. There were 3 pregnancies in the Yasmin™ group and 3 in the Marvelon group, giving a corrected Pearl Index of 0.41 for both groups and a Pregnancy Ratio of 1.12% for Yasmin™ and 1.18% for Marvelon®. All of the pregnancies were considered user failures. One pregnancy in the Yasmin™ group resulted in a healthy baby boy, one had an induced abortion, and the other was lost to follow-up.

US Study 96049 (Pivotal Report 98180) was a six center, open-label, non-randomized, single-group, Phase III study in which 326 reproductive aged women received Yasmin™ for up to 13 cycles. 222 subjects completed 13 cycles. 54% of subjects switched from other oral contraceptives at baseline. 87% of subjects were Caucasian. There was one pregnancy in the third cycle of use, giving a corrected Pearl Index of 0.407 and Pregnancy Ratio of 0.455%. The subject had missed her pill on cycle day 5 and took 2 pills the following day. She elected to terminate the pregnancy.

Supportive European Study 93044 (Report AJ06) was a multi-center, open-label, parallel group, Phase III study in which 2069 reproductive aged women were randomized and received Yasmin™ (n=1657) or Marvelon® (n=412) for up to 13 cycles. 1288 women completed 13 cycles of Yasmin™ use and follow-up. There were 10 pregnancies during Yasmin™ treatment and 1 during Marvelon® treatment. 4 additional pregnancies occurred in Yasmin™ subjects and 2 in Marvelon® subjects before or after the treatment phase. The corrected Pearl Index for Yasmin™ was 0.71 and corrected Pregnancy Ratio 0.84%.

The overall results of all efficacy studies in which at least 15 women at risk of pregnancy were exposed to study drug for at least 6 cycles yielded corrected Pearl Indices ranging from 0 to 0.70 (0.71 corrected) for Yasmin™ and 0 to 0.41 for the major comparator, Marvelon®.

The most common reason for discontinuation from Yasmin™ study medication was adverse events (9% [n=252]). A similar proportion of subjects prematurely discontinued due to "other" reasons (8% [n=243]). The AEs reported with Yasmin™ were similar in nature and incidence to AEs reported with other currently marketed OCs.

There was one death reported in all studies. Subject 228 (supportive Study 93044), a 28 year old who had taken Yasmin™ for five months, died suddenly of cardiac arrest from a severe post-streptococcal myocarditis with extensive inflammatory infiltrates. Serious adverse events, including 1 pulmonary embolism (Subject 384/Study 92052), were reported for 2% (n=54/3317) of all DRSP treated subjects. 2% (n=26/1123) of subjects treated with active controls also experienced serious adverse events. The adverse event that occurred most often among DRSP treated subjects in all studies was headache.

2.0 BACKGROUND

The proposed product is a combination preparation consisting of fixed doses of two female steroid hormones intended for oral contraception.

Drospirenone (DRSP), a new molecular entity, is a novel progestin, a derivative from 17α-spirolactone. Like natural progesterone, it possesses progestogenic and aldosterone-antagonistic (antimineralocorticoid) properties. In addition, studies with DRSP show antiandrogenic activity and no significant androgenic, estrogenic, glucocorticoid, or antiglucocorticoid activity.

Ethinyl estradiol (EE) belongs to the class of estrogens and is a frequently used estrogen in oral contraceptive products.

2.1 Regulatory history

At a Phase III meeting held on February 12, 1997, it was determined that the completed European Phase III clinical trial (Study 92052/Report A151) appeared adequate in terms of reported observed cycles and available safety data to support the filing of an NDA. Because this study population was approximately 96% Caucasian, a second US trial (Study 96049/Report 98180 conducted under [redacted] recommended to include a more varied ethnic mix.

Reviewer's comment
The study population for 96049 was 87% Caucasian. Despite lack of significant information for use of this product in other ethnic groups, there is no known reason to suspect a difference in contraceptive efficacy in other groups.

At a pre-NDA meeting held on January 28, 1999, it was determined that the overall proposal for the NDA application appeared acceptable, that additional biopharmaceutics special population and drug interaction studies should be considered, and that additional toxicology studies will be requested as a Phase IV commitment if they are needed.

2.2 Clinical background and proposed mechanism of action

Oral contraceptives are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, without missing pills, the chance of becoming pregnant is less than 1.0%. Ovulation inhibition studies established that ovulation was inhibited in some subjects receiving 1 mg DRSP and in all subjects receiving 2 mg DRSP. Dose finding studies found the 2 mg dose to be the threshold dose for inhibition of ovulation. However, 50% of subjects showed follicular maturation with the 2 mg dose, and a small number of subjects ovulated. The 3 mg dose inhibited follicular activity in 91% of subjects and no subject ovulated. 3 mg was, therefore, further developed in combination with 0.030 mg EE as an oral contraceptive.

It has been suggested that fluid retention and the occasionally observed hypertensive effect of hormonal contraceptives is a result of the fact that the synthetic estrogens in combination oral contraceptives (COCs) lead to sodium retention, partly by activation of the renin-angiotensin-aldosterone system, which is not antagonized by the synthetic progestogens in these preparations. In the spontaneous menstrual cycle of women, the sodium-retaining effect of estrogen is opposed by the natriuretic properties of progesterone.

DRSP, a 17α-spirolactone derivative, is a novel progestogen that has been found in preclinical and human pharmacological studies to possess a combination of progestational and aldosterone-antagonistic properties, a profile similar to that of natural progesterone. In addition, preclinical animal and *in vitro* studies have shown antiandrogenic activity and no estrogenic effects.

The sponsor proposes that this new COC formulation, containing DRSP 3 mg as the progestogen and EE 30 μg as the estrogen, may enhance patient acceptability and efficacy by reducing problems associated with noncompliance and increasing the margin of safety among women using oral contraceptives.

2.3 Human pharmacology, pharmacokinetics, and pharmacodynamics

Whereas EE has previously been extensively studied and characterized, this review will focus primarily on DRSP.

17 studies using DRSP alone or in combination with EE present data on bioavailability, metabolism and mass balance, PK linearity, single and multiple dose pharmacokinetics, food effect, pharmacokinetic interaction of DRSP and EE, distribution of DRSP into breast milk, percutaneous absorption, cytochrome inhibition, and the effect of DRSP on EE metabolism.

DRSP is well-absorbed after oral administration, with absolute bioavailability of 77 ± 14%. Maximum plasma concentrations were reached on average between 2.2 and 2.7 hours after oral administration of the combination of 3 mg DRSP and 0.030 mg EE. On the first day of administration in treatment cycles 1 and 3, maximum serum concentrations of DRSP were on average 36.5 and 39.6 ng/mL, respectively. On the last day of administration in treatment cycles 1 and 3, maximum serum concentrations were 59.5 and 60.4 ng/mL, respectively, indicating accumulation of DRSP during the treatment cycles. Mean half-lives were 28.3 hours and 29.5 hours in cycles 1 and 3, respectively. Maximum concentrations of EE in serum were reached on average between 2.2 and 2.6 hours after drug administration. Mean maximum concentrations were between 108 and 122 pg/mL after the first tablet and about 145 pg/mL after the last tablet in both treatment cycles. There is no indication of any pharmacokinetic interaction between DRSP and EE.

Maximum serum concentrations of DRSP are reached later and reduced on average to 62% (range 30-103%) after concomitant food intake compared with drug intake after 10 hours of fasting. However, the relative bioavailability and terminal half-life remained unchanged. In clinical trials, dosing was given without regard to meals.

DRSP is extensively metabolized according to a mass-balance study using radioactively labeled DRSP. At least 20 different metabolites were observed in urine and feces, and only trace amounts were excreted unchanged. Two major metabolites were the free acid of DRSP and the 4,5-dihydro-DRSP-3-sulfate. About 37-47% of the metabolites were excreted as glucuronide and sulfate conjugates. Radioactivity was 80% excreted after 10 days. The feces to urine excretion ratio was 1.2 to 1.4. After intravenous administration, the mean overall recovery was 32.2 ± 3.2% of the dose in urine and 44.1 ± 9.2% of the dose in feces. After oral administration, the recoveries were 38.5 ± 4.7% of the dose in urine and 44.3 ± 6.1% in feces.

The pharmacokinetics of DRSP are dose-proportional and unaffected by alterations in SHBG and CBG levels. SHBG concentrations in serum increased approximately 4-fold during the first treatment cycle and approximately 1.6-fold during the third treatment cycle. SHBG concentrations decreased slowly during the drug-free intervals between cycles, resulting in higher levels at the beginning of subsequent treatment cycles compared to cycle 1. CBG increased by a factor of 2.2 during the first treatment cycle and by a factor of 1.4 during the 3rd treatment cycle. SHBG and CBG concentrations in serum decline biphasically after cessation of treatment, and physiological steady state concentrations are reached within 4 to 6 weeks.

A study in lactating women shows a maximum DRSP concentration of 13.5 ± 11.7 ng/mL in breast milk (compared to 30.8 ± 14.4 ng/mL in serum at 2.8 ± 1.3 hours after oral administration of Yasmin™. The ratio of AUC_{0-48h} in breast milk versus serum was on average 0.23 ± 0.09. The average DRSP concentration in breast milk 24 h after dosing was 3.7 ± 1.9 ng/mL. The estimated daily dose reaching the baby was 3 µg DRSP, or 0.1% of the daily maternal dose, assuming a daily ingestion of about 800 mL breast milk.

Reviewer's comment
Clinical relevance of this dose of DRSP in infants in unknown.

In vitro studies with high concentrations of DRSP revealed almost no effect on substrate turnover of CYP 2D6 or CYP1A2. DRSP showed minor inhibition of CYP1A1, moderate inhibition of CYP3A4 (reversible) and CYP2C9, and relatively more potent inhibition of CYP2C19. The concentrations needed to inhibit 50% CYP450 enzyme activity in vitro was about 266 (CYP2C19), 3186 (CYP 2C9), and 2743 (CYP3A4) times higher than the C_{max} of free DRSP in human serum at steady-state after administration of Yasmin™.

DRSP has dose-dependent antagonistic effects on aldosterone, with increased urinary sodium excretion and significantly increased urinary Na/K ratios. However, no changes in the urinary K concentration were seen with a 10 mg DRSP dose. DRSP preparations did not affect electrolyte levels in plasma, indicating that an effect on serum K concentrations or on water balance is unlikely. Effects were only noted at the 40 and 160 mg doses, which are about 13-53 times greater than the recommended 3 mg dose of DRSP in the Yasmin™ tablet intended for market. The relative potency (mg/kg) of DRSP is about 8 times higher than that of spironolactone. However, in clinical practice, spironolactone dosages range from 25 to 400 mg/day, 8-130 times the dose of DRSP recommended for inhibition of ovulation. Therefore, spironolactone is expected to have 1-17 times the antialdosterone activity of Yasmin™ in clinical practice.

2.4 International Marketing Experience

Drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 30 *ug* has not been marketed anywhere in the world.

3.0 CLINICAL STUDY 92052 (Report A151): European "pivotal" Phase 3 Efficacy and Safety Study

3.1 Title

A multicenter, open-labeled, randomized study on cycle control and tolerance of SH T 470 FA (Yasmin™) in comparison with Marvelon® in up to 26 cycles under long-term contraceptive use

3.2 Study objective

The aim of the study was to obtain data on the contraceptive reliability, cycle control, and tolerance (including blood pressure, heart rate, and body weight) of SH T 470 FA (Yasmin™) in long-term contraceptive use (up to 26 cycles) in comparison to Marvelon®, a marketed oral contraceptive containing the same dose of EE (30 μg) with a different progestin, 0.15 mg desogestrel.

3.3 Study design

This was an open-label randomized, multicenter trial, with two equal treatment groups. One group received Yasmin™ tablets and the other received Marvelon® tablets, both according to the same schedule, one daily for 21 days followed by a 7-day tablet free interval, for 26 cycles of use, starting on the first day of menstrual bleeding.

3.4 Study population

A total of 940 subjects were screened at 26 centers. There were 40 screening failures. 900 subjects were randomized, 450 per treatment. The number of screened subjects per center ranged from 6 to 83. 8 Yasmin™ subjects and 5 Marvelon® subjects were listed only and did not receive study drug. The intent to treat (ITT) population consisted of 887 subjects (442 using Yasmin™ and 445 using Marvelon®). The valid case analysis (VCA) population consisted of 718 subjects (365 using Yasmin™ and 353 using Marvelon®).

627 subjects completed the study as planned (26 cycles plus follow-up phase), 310 using Yasmin™ and 317 using Marvelon®. A total of 138 subjects using Yasmin™ and 132 using Marvelon® dropped out of the study prematurely. Data on 3 subjects are missing.

Study Population			
Total screened	940		
Screening failures	40		
		Yasmin™	Marvelon®
Randomized	900	450	450
Listed only (Received no study drug)	13	8	5
Intent to Treat	887	442	445
Total drop-outs after randomization	270	138	132
Completed 26 cycles and follow-up	627	310	317
Valid Cases Analyzed	718	365	353
Missing data	3	2	1

Contraceptive effectiveness results were reported using the ITT population, whereas cycle control was reported with regard to the VCA population.

Each cycle was assessed for validity according to the number of tablets taken. Any cycle with ≤ 4 pills taken was considered not valid and all following cycles not valid. Cycles with 5-13 pills taken was not valid and the next cycle not valid. Any cycle with 14-19 pills taken was not valid but all subsequent cycles with correct pill-taking were valid. Any cycle with 23-42 pills taken was not valid. If the pill-free period was 0-5 days or 9-23 days, the cycle was not valid, and the following cycle was also not valid. If the pill-free period was >23 days, the cycle and all following cycles were not valid. Any cycle length of < 26 days or > 30 days, excluding the first and last cycles, was considered not valid. Whereas the primary target variable for the analysis was the occurrence of intracyclic bleeding during the 2nd to 6th treatment cycles, any subject was considered a valid case if her treatment cycles 1 to 6 were all valid.

Inclusion criteria

Any healthy woman was admitted to the study after having given her written, informed consent as long as the following criteria were satisfied:

1. Age between 18 and 35
2. Initially, smokers could only smoke up to 10 cigarettes per day, but an amendment on Jan. 14, 1993 deleted this inclusion criterion. However, smokers over age 30 were not admitted.
3. Both de novo users and women switching from another oral contraceptive, excluding those containing ZK 30595(drospirenone) and desogestrel, were admitted. No washout phase was observed.
4. Willingness not to use any other hormone preparations during treatment
5. Following delivery, abortion, or lactation, subjects were admitted only after the first normal, biphasic cycle.
6. Pregnancy was ruled out before the first tablet was taken by means of a β-HCG test.
7. Care was taken to admit only those women who were prepared to take the study medication over the planned duration of the study and willing to undergo regular medical and self-examinations (cycle, weight checks) according to the protocol.

Ethnicity was of no consequence in the study.

Reviewer's comment

There was no requirement for subjects to be at risk for pregnancy.

Exclusion criteria

1. Pregnancy and lactation
2. Liver diseases (acute and chronic progressive liver diseases, disturbances of bile secretion and drainage (cholestasis, including a history thereof), past or present liver tumors, Dubin-Johnson syndrome, Rotor syndrome, idiopathic jaundice and severe pruritis in a previous pregnancy or after sex hormone treatment, all three forms of porphyria)

3. Vascular and metabolic diseases (past, present, or family history of thromboembolic processes (thrombosis, embolism) in veins or arteries (particularly stroke, cardiac infarction), including thrombophlebitis, disturbed coagulation with a tendency to clotting (thrombosis), certain cardiac disorders--hypertension (≥ 140/90 mm Hg) requiring therapy, diabetes mellitus, sickle cell anemia, disturbances of lipometabolism)
4. Tumors (all malignant tumors, i.e. mammary or endometrial carcinoma) and benign tumors of the liver and pituitary, including after treatment or a suspicion thereof)
5. Other diseases (obesity: 20% above normal weight according to Broca (height in cm minus 100, expressed in kg), epilepsy, migraine accompaneé, gestational herpes, otosclerosis with worsening in a previous pregnancy, acute visual disturbances or other sensory disorders, endometriosis, genital bleeding of unknown origin)
6. Cervical smear for cytological examination with Pap classification > CII
7. Genital infection (i.e., chlamydia trachomatis, gonorrhea)
8. Use of ZK 30595 or desogestrel-containing preparations in the last cycle preceding the treatment,
9. Parenteral depot contraceptives in the last six months prior to the study,
10. The use of other contraceptive methods, excluding the use of condoms for AIDS prophylaxis,
11. Smokers over the age of 30
12. Alcohol, drug, and medicine abuse
13. Use of preparations which experience had shown affect the activity of hepatic enzymes (e.g., barbiturates, rifampicin, anti-epileptics) or absorption (e.g., antibiotics)
14. Use of diuretics or preparations for the treatment of premenstrual syndrome

Demographics

- The mean age of Yasmin™ users was 26.5 ± 4.6 years and of Marvelon® users was 26.0 ± 4.8 years.
- The mean weight was 63.1 ± 9.1 kg for Yasmin™ users and 62.5 ± 9.4 kg for Marvelon® users.
- The mean body mass index (BMI) was 22.6 ± 2.8 kg/m$^{2\ in}$ Yasmin™ users and 22.2 ± 2.7 kg/m$^{2\ in}$ Marvelon® users.
- With the exception of 7 Hispanic subjects in the Yasmin™ group and 2 Black and 2 Asian subjects in the Marvelon® group, all other subjects were Caucasian (98% of Yasmin™ users and 99 % of Marvelon® users).
- 50% of Yasmin™ users and 54% of Marvelon® users had no history of previous pregnancies.
- 15% of Yasmin™ users and 19% of Marvelon® users reported absence of monthly bleeding in the 6 months before treatment, and 8% and 7%, respectively, reported intracyclic bleeding.
  Reviewer's comment
  Although not addressed by the sponsor, it is likely that use of oral contraceptives prior to the study may have influenced these bleeding patterns.
- 12% of Yasmin™ users and 14% of Marvelon® users reported dysmenorrhea.
- 24% of Yasmin™ users and 22% of Marvelon® users were current smokers, smoking a mean of 9 to 11 cigarettes per day in both groups.
- 17% of Yasmin™ users and 15% of Marvelon® users reported premenstrual syndrome in the 6 months before treatment.
- 73% of Yasmin™ users and 69% of Marvelon® users had taken other oral contraceptives in the month prior to the study and switched to the study drug without a washout period.
  Reviewer's comment
  Although a washout period of 2 months without hormonal contraceptives is preferred prior to participation in a contraceptive trial, the 26 cycle duration of this study is adequate to compensate for the lack of such a washout period.

3.5 Screening period

Informed consent was obtained and a medical and surgical history and general physical and gynecological examination performed, including breast examination, and cervical cytology smear for all subjects who did not have a cervical smear in the preceding 3 months. Blood pressure and heart rate were recorded, urine was examined for glucose, and blood was sampled for general chemistry and hematology determinations.

The subjects were asked to record their body weight on 3 consecutive days in the week prior to the next expected menses.

3.6 Treatment period

A β-HCG pregnancy test was performed prior to taking the first tablet, and on absence of withdrawal bleeding during treatment.

The treatment phase began with the first day of menstrual bleeding and ended on day 28 of the last treatment cycle (cycle 26). The tablets were taken in the normal manner for oral contraceptives: 21 days of tablet taking, followed by a 7-day tablet-free interval. Tablet taking was resumed on the same day of the week, 4 weeks later, as the previous blister pack had been started.

Subjects were also required to keep a menstrual chart, which was reviewed by the investigator at each visit. They were also required to weigh themselves weekly and to keep a record of the weights in weight charts provided to them.

Visits during the treatment phase took place between days 14 and 21 in the 2nd or 3rd, 6th, 9th, 12 or 13th, 15th, 18th, 21st, 24th, and 26th cycles. Blood pressure and heart rate were measured and recorded at each visit. Concomitant therapies and any spontaneously reported adverse events were recorded. Use of condoms for AIDS prophylaxis was also recorded at each visit.

Possible premenstrual syndrome (PMS) complaints were recorded as such if the investigator determined that the temporal relationship of the complaint to the subject's menstrual bleeding indicated that the complaint was one related to PMS and the leading symptoms were documented. The PMS complaints were also specified as PMS on the Adverse Event (AE) page.

Reviewer's comment
In an open label trial, such subjective complaints as PMS symptoms are very difficult to interpret. In this NDA, the sponsor makes no comparative claims of superior tolerability in this regard and would have to conduct blinded studies in order to do so.

At visits 3 (cycle 2 or 3), 6 (cycle 12 or 13), and 11 (cycle 26 or at premature termination), blood was taken for general chemistry and hematology parameters, and urine was tested for glucose.

The gynecological examination was repeated at visits 4 (treatment cycle 6), 6 (cycle 12 or 13), 8 (cycle 18) and 11 (cycle 26 or premature termination), including breast examination and a cervical smear for cytology. In The Netherlands, the cytology smear was performed only at visits 6 and 11.

If the subject wished to continue oral contraceptives following the end of the treatment phase, she was free to do so. If she desired pregnancy after treatment or after premature termination of treatment, she was requested to give her consent to following the course and outcome of the pregnancy.

The follow-up phase was originally scheduled to include the 35 days after the end of the last treatment cycle (42 days following the last tablet intake). Protocol Amendment 2 (17 Aug., 1993) extended the follow-up to 3 months following the last tablet intake.

The first follow-up visit (visit 12) took place 35 days after completion of the 26th treatment cycle. If withdrawal bleeding failed to take place after the end of the study medication, a β-HCG pregnancy test was to have been performed. Weight and menstrual charts were maintained during the first follow-up phase. Blood pressure and heart rate were recorded at visit 12. Any spontaneously reported adverse events or changes in concomitant medications were recorded.

Three months after the last tablet intake, the subject was either contacted by telephone or visited the investigator. She was asked about contraception, menses, and whether any adverse events had occurred. If a pregnancy had occurred since the last visit, the details of the pregnancy were recorded.

Reviewer's comment
Pregnancy tests were not routinely performed at the final visit, and were performed only if withdrawal bleeding did not occur. However, given that 310 subjects completed 26 cycles and a follow-up visit, the lack of routine pregnancy testing at the final visit should not significantly affect evaluation of contraceptive efficacy.

3.7 Statistical Procedures

The number of subjects with intracyclic bleeding at least once during cycles 2 to 6 was compared between the treatments using the χ^2 test. This test was two-sided with a significance level α of 5%.

The secondary target variables, occurrence of intracyclic bleeding during the 2nd to 13th, 2nd to 18th, and 2nd to 26th treatment cycles, were analyzed exploratively using the two-sided χ^2 test and a comparison-wise significance level α of 5%.

In an additional exploratory analysis in order to assess a possible center effect, both the primary and secondary target variables were analyzed using the Mantel-Haenszel test controlling for centers. These tests were also two-sided with a comparison-wise significance level α of 5%.

Missing data were not replaced.

In addition to the planned analyses, the Pearl Index and the corrected Pearl Index were calculated for the study using the formula Pearl Index = 1300 x number of pregnancies / number of cycles. Each pregnancy occurring in the study was assessed by the international trial manager to determine whether the conception occurred during treatment. All pregnancies under treatment were included in the nominator. All cycles in which at least 19 tablets were taken were included in the denominator. The sponsor believes this is a conservative approach since shortened cycles are not counted in the denominator. The corrected Pearl Index includes all cycles in which at least 19 tablets were taken and in which no condom use was documented in the denominator.

Reviewer's comment

- **Pearl Index =1300 x number of pregnancies / number of cycles. The corrected Pearl Index is 1300 x number of pregnancies / number of cycles without other contraception. This index has commonly been accepted as the primary efficacy endpoint in contraceptive trials.**
- **Excluding cycles in which less than 19 tablets were taken in the denominator and not excluding pregnancies occurring in those cycles from the numerator would not have an unfair influence on the Pearl Index.**

For each of the periods, cycles 1 to 6, cycles 1 to 13, and cycles 1 to 26, the ratio of the number of pregnancies occurring during the period divided by the number of women taking at least 19 tablets in each cycle of the period were calculated in percent. These ratios were also given excluding women who used any condom during the period.

Pregnancy Ratio = 100 x number of pregnancies / number of women completing the designated number of cycles.

An intent-to-treat (ITT) analysis was performed for all target variables. In addition, a valid case analysis (VCA) was done for the primary target variable and the other efficacy variables. Subjects that were randomized but did not receive any study medication were classified as "listing only".

No interim analysis was performed.

Unplanned exploratory analyses were performed for absolute weight change in the first year, percent weight change in the first year, absolute weight change in the second year, and percent weight change in the second year. A two-sided t-test for independent samples and a significance level α of 5% were used.

3.8 Evaluation Criteria

The sponsor states that the study protocol defined in its "Target variables" the contraceptive reliability of Yasmin™ as the first objective. However, the primary target variable for the statistical analysis was the occurrence of intracyclic bleeding during the 2nd through 6th treatment cycle. All bleeding from day 4 to day 21 of tablet intake, regardless of intensity, was defined as intracyclic bleeding.

The occurrence of intracyclic bleeding during the 2nd to 13th, 2nd to 18th, and 2nd to 26th treatment cycles were analyzed as secondary target variables.

3.9 Withdrawals and compliance

Premature discontinuation of study		
	Yasmin™	Marvelon®
Total premature discontinuations from study (26 cycles + follow-up)	138	132
Premature discontinuations of medication (26 cycles)	135	129
Listed only (never received study drug)	8	5
Pregnancy	3	3
Adverse event	49	42
Protocol deviation	4	6
Withdrawal of consent	1	4
Other:	78	75
Desire for pregnancy	29	29
Lost to follow-up	15	13
Noncompliance	7	5
Desire to stop medication	6	5
Personal reasons	5	11
Loss of partner	5	1
Moved away	5	9
Partner sterilized	2	1
Partner against participation	2	1
Lost study medication	2	0

Subjects had the right to withdraw from the study at any time without stating reasons. If the reason was given, it was to be entered in the case report form. If the trial medication had already been administered at the time of refusal, the subject was encouraged to return for follow-up, and any unused tablets and empty containers were to be returned. In addition, the following were reasons for immediate termination of study participation:

1. pregnancy
2. signs of venous inflammation or blood clots , before scheduled surgery and because of prolonged immobility
3. new onset of migraine headaches or headaches occurring more frequently with unusual severity
4. sudden sensory disturbances (visual, auditory, etc.)
5. motor disturbances (particularly paralysis)
6. repeatedly measured increases in blood pressure (>140/90 mm Hg)

7. occurrence of liver inflammation, jaundice, itching over the entire body, disturbances of bile drainage (cholestasis), and unusual liver function values
8. new onset of epileptic seizures under the medication
9. repeated, excessive persistent intracyclic bleeding
10. unusual upper abdominal complaints which did not spontaneously disappear

Reasons for termination were to be documented in detail in the CRF. In the event of premature discontinuation due to an adverse event or due to abnormal laboratory values the subject was to be kept under observation for 3-4 weeks or until the findings had normalized.

Protocol deviations were detected in 228 out of 900 randomized subjects, 99 using Yasmin™(22%) and 129 using Marvelon®(29%). Not all protocol deviations led to an exclusion from VCA and several deviations may have been detected in one subject. The majority of protocol deviations were use of antibiotic treatment during the study and treatment schedule violations.

Under ITT analysis, 39% of Yasmin™ users and 35% of Marvelon® users made at least one mistake in pill-taking, including cases with use of >21 pills. At least one pill-taking mistake occurred in 4% of cycles for both groups. If a pill was missed, only one pill was missed in most cases. In 3% of Yasmin™ cycles and 4% of Marvelon® cycles, a pill-free interval of other than 7 days was observed. A shortened pill-free interval was more common than a lengthened pill-free interval.

3.10 Efficacy analysis

Among the 442 subjects taking Yasmin™ and the 445 subjects taking Marvelon®, there were 3 pregnancies in each study group, giving a corrected and uncorrected Pearl Index of 0.41 for both Yasmin™ and Marvelon®.

The Pregnancy Ratio for cycles 1 to 6 was 0.26% for both groups (1 pregnancy in each group). The corrected pregnancy Ratios for cycles 1 to 6 were 0.26% for Yasmin™ and 0.27% for Marvelon®. For cycles 1 to 13, there was still only one pregnancy in each group, giving a Pregnancy Ratio of 0.29% for Yasmin™ and 0.30% for Marvelon® and corrected Pregnancy Ratios of 0.30% and 0.32%, respectively. For cycles 1 to 26, there were 3 pregnancies in each group, giving a Pregnancy Ratio of 1.08% for Yasmin™ and 1.09% for Marvelon® and corrected Pregnancy Ratios of 1.12% and 1.18%, respectively.

Summary of pregnancies in Yasmin™ users

1. A 26 year old former OC user with 2 previous births and no abnormalities completed 25 cycles of Yasmin™ use. Conception occurred between days 5 and 17 of cycle 25. The subject stated that she desired pregnancy, she was under a period of occupational stress, and she may not have taken her pills regularly. She was lost to follow-up.
2. A 26 year old OC starter with one previous birth completed 17 cycles, missing one pill in cycle 2, 3 pills in cycle 6, and 1 pill in cycle 7. The pill-free interval was 8 days in the pre-conception cycle 17, and she missed 4 pills in cycle 18. She conceived on day 8 of cycle 18. She underwent an induced abortion.
3. An 18 year old nulligravid woman with 2 years of prior OC use and history of polycystic ovary syndrome completed 3 cycles. The pill-free interval was 6 days in cycles 1 and 3. On day 11 of cycle 4, she vomited within 2 hours after pill intake. She also reported delayed pill-intake several times by 12-16 hours. She conceived on day 26 of cycle 4. She continued the pregnancy and delivered a healthy boy.

Reviewer's comments

The following subjects who were randomized to Yasmin™ treatment may have been at low risk or not at risk for pregnancy:

1. **One subject did not have a pregnancy test before her first dose of study medication because she had not had sex for 6 weeks.**
2. **3 subjects were noted to be virgins**

3. **1 subject previously underwent in vitro fertilization and one underwent ovulation induction, both suggesting a history of infertility**
4. **92 Yasmin™ users reported no use of contraception in the month prior to study, and no information is provided as to whether they were sexually active.**
5. **14 Yasmin™ users (0-2.5% of subjects in each cycle) used condoms for STD prevention during the trial**

Even if subjects not at risk of pregnancy were excluded from the efficacy analysis, the pregnancy rate would be acceptable.

After discontinuation of treatment 20 pregnancies were reported in 18 Yasmin™ users, including 2 subjects who reported two pregnancies each.

- 13 of these 20 pregnancies resulted in births of healthy babies 10 to 26 months after last study medication.
- One patient experienced an intrauterine fetal death due to a viral infection and delivered 9 months after last study medication at 7 months gestation. The delivery was complicated by cardiac arrest of the mother due to amniotic fluid embolism. She was successfully resuscitated, and subsequently had another pregnancy and delivered a healthy baby.
- One pregnancy was diagnosed in pregnancy week five exactly five weeks after her last pill and subsequently resulted in a missed abortion. Her second pregnancy resulted in a healthy baby delivered 17 months after her last study medication.
- Two subjects elected to have induced abortions, and 3 were lost to follow-up.

The sponsor reports that none of these pregnancies were conceived while taking the study medication. 11 of these subjects had discontinued the study early, and 7 of them had indicated a wish for pregnancy at the time of discontinuation.

Reviewer's comment

For 7 of the above pregnancies, inadequate information is provided regarding gestational dating parameters to confirm the estimated dates of conception after discontinuing the study drug.

Intracyclic bleeding

Intracyclic bleeding was defined as any bleeding between day 4 and day 21 of pill intake. 8% of subjects in both treatment groups reported intracyclic bleeding during the 6 months prior to the start of the study. At least one intracyclic bleeding during the treatment phase was reported by 56% of Yasmin™ users and by 58% of Marvelon® users. Intracyclic bleeding occurred more often at the beginning of both treatments, particularly in the first treatment cycle (28% of Yasmin™ users and 25% of Marvelon® users), and dropped continuously thereafter. After 6-7 cycles, intracyclic bleeding rates were comparable to or lower than rates reported for the 6 months before treatment. In cycle 26, 6% of Yasmin™ users and 10% of Marvelon® users reported intracyclic bleeding. Most intracyclic bleeding episodes were described as scanty.

At least one episode of intracyclic bleeding from cycle 2 to 6 (Primary target variable) was reported in 30.79% of Yasmin™ subjects (ITT) and 28.75% of Marvelon® subjects (ITT); p = 0.527. Secondary target variables (cycle 2 to 13, 18, and 26) also showed no significant differences between groups.

Withdrawal bleeding

The majority of subjects in both treatment groups had a withdrawal bleed of 4 to 7 days duration. The duration of withdrawal bleeding in cycle 26 is not accurately represented because the bleeding days were only documented until day 28, even if the bleeding lasted longer. In cycles 1 to 25, 9-14% of Yasmin™ users (and 9-13% of Marvelon® users) had 1- 3 days of withdrawal bleeding, 83-88% of Yasmin™ users (and 84-89% of Marvelon® users) had 4 - 7 days of withdrawal bleeding, and 3-4% of subjects in both groups had more than 7 days of withdrawal bleeding.

In cycles 2 to 26, 12-18% of Yasmin™ users (and 11-16% of Marvelon® users) reported only scanty withdrawal bleeding. 62-82% of Yasmin™ users (and 71-84% of Marvelon® users) reported both scanty

and normal/excessive withdrawal bleeding, and 4-10% of Yasmin™ users (and 3-9% of Marvelon® users) reported only normal/excessive withdrawal bleeding).

In the follow-up phase, 77 Yasmin™ users and 59 Marvelon® users stopped OC use and reported spontaneous cycles. The mean cycle length during follow-up was 31 days in the Yasmin™ group and 32 days in the Marvelon® group. 56% of Yasmin™ users and 49% of Marvelon® users had a post-treatment cycle of 26 to 31 days.

Amenorrhea occurred in 2% of Yasmin™ treatment cycles and 1% of Marvelon® treatment cycles. 17% of Yasmin™ subjects and 11% of Marvelon® subjects had at least one episode of amenorrhea during the study.

Dysmenorrhea was reported by 12% of Yasmin™ subjects and 14% of Marvelon® subjects at baseline and occurred in 4% of treatment cycles in both groups. The frequency of dysmenorrhea decreased with increased duration of treatment in both groups. In the follow-up period, dysmenorrhea recurred in 18% of Yasmin™ subjects and 22% of Marvelon® subjects.

394 Yasmin™ subjects were contacted 3 months after the end of the study. 287(73%) had chosen oral contraceptives, and 77(20%) reported no contraceptive use at all. A total of 103 subjects (95%) out of 108 reported return of natural menses, and 5 subjects (5%) had no menses. Of these, one had induced menstruation, one had no induced menstruation, and no data was available for 3 subjects.

Reviewer's comment
In this open label trial, bleeding patterns and dysmenorrhea appear similar with Yasmin™ and with the approved comparator, Marvelon®.

3.11 Safety analysis

There were no deaths during the study.

327 out of 442 Yasmin™ users (74%) reported 1880 adverse events. 346 out of 445 Marvelon® users (78%) reported 1760 events. The most frequently reported adverse events were the following:

Adverse event	Yasmin™	Marvelon®
Headache	19.9%	20.4%
PMS	17.9%	19.8%
Breast pain	14.9%	11.7%
Abdominal pain	12.0%	12.1%
Vaginal moniliasis	9.7%	9.7%
Flu syndrome	9.5%	7.9%
Nausea	7.5%	5.8%

19 of 442 Yasmin™ users (4.3%) and 13 of 445 Marvelon® users (2.9%) experienced serious adverse events (SAEs) during treatment. Another 3 (0.7%) Yasmin™ users and 2 (0.5%) Marvelon® users reported SAEs during follow-up.

SAEs during Yasmin™ treatment:

1. A 34 year old subject had a cholecystectomy for cholelithiasis planned prior to the study. It was performed two weeks after the start of treatment, and the postoperative course was uneventful. (No causal relationship)
2. A 25 year old subject underwent a cholecystectomy for acute cholelithiasis after 5.5 months of treatment. The postoperative course was uneventful. (No causal relationship)

3. After 13 months of study medication, a 32 year old subject underwent a laparoscopic cholecystectomy for gallstones, which presented as low back pain. Treatment was not interrupted. (Causal relationship unlikely)
4. After 6 weeks of treatment, a 32 year old Caucasian subject weighing 56 kg and with no smoking history was hospitalized 1 week for intravenous antibiotics for a urinary tract infection. 6 weeks later she was again hospitalized and treated with intravenous antibiotics for suspected pyelonephritis and biliary lithiasis. A cholecystectomy was performed. Three weeks later, a pulmonary embolus was suspected. Physical examination, chest X-ray, doppler sonography of the legs, and ventilation-scintigraphy of the lung were all negative. The perfusion-scintigraphy was positive. The patient was treated with heparin and recovered completely. She did not stop the study medication until after she had completed the heparin therapy. The pulmonary embolus was rated as possibly related to the study drug. The patient had completed 4 months of treatment with the study drug. (No causal relationship of cholecystectomy, possible causal relationship of suspected pulmonary embolus)
   Reviewer's comment
   Although there were no cases of cholecystectomy in the Marvelon® group, these 4 cases of gallbladder disease requiring cholecystectomy (one planned prior to start of study medication) are not unusual in a hormonal contraceptive trial of this size. Gallbladder disease and pulmonary embolism are both known AEs associated with hormonal contraceptive use.
5. A 25 year old subject with known fibroadenoma of the left breast at enrollment, diagnosed 1 month prior to treatment, underwent excision 20 months later without complications. Histology was benign. Treatment with the study drug was not interrupted. (No causal relationship)
6. After 13 months of treatment, a 29 year old subject was hospitalized 6 days for excision of a breast tumor. Histology was benign. (Causal relationship unlikely)
7. A 28 year old subject had a Class III Pap after 18 months of treatment. 10 weeks later, she had a Class IVA Pap. "Hysteroscopy, abrasio, and laser-conisation" were performed. Histology showed moderate to severe dysplasia with beginning transition to carcinoma in situ. The sponsor requested that the subject be discontinued from participation. Three previous Pap smears were Class II. (Causal relationship unlikely)
   Reviewer's comment
   Given that cervical dysplasia is not an uncommon finding among sexually active women and that the false-negative rate for a single Pap test (e.g., the cytology result at screen) is 10-25%, the finding of a Class IVA Pap in this one individual does not suggest an effect of Yasmin™ on cervical cytology.
8. After 16 months of treatment, a 19 year old subject experienced right sided pelvic pain, fever and asthenia. She was hospitalized with suspected pelvic inflammatory disease and treated with antibiotic triple therapy. A further hospitalization was planned 2 weeks later for a laparoscopic investigation, and an appendectomy and cystectomy of the right ovary were performed. Histology revealed a benign cyst. In the follow-up period, two months after treatment, an ultrasound examination showed an adnexal mass, and a repeat ultrasound one month later was normal. (No causal relationship)
9. After 17 months of treatment, a subject was hospitalized one week for depression. The subject did not want to give details about her condition, and she was then lost to follow-up. (Causal relationship unknown)
10. A 19 year old subject discontinued the study after four months of treatment due to an accepted pregnancy. An ovarian cyst was diagnosed at that time. 9 months later, after an uneventful pregnancy and delivery of a healthy child, she underwent a laparoscopic "adnexexstirpation". (No causal relationship)
11. A 28 year old subject underwent surgery for an anal fistula after 11 weeks of treatment and recovered. The study drug was continued. (No causal relationship)
12. A 31 year old subject had acute loss of hearing in the pretreatment phase and was hospitalized for 10 days. She started the study drug 3 weeks later. After 6 weeks, the sponsor required that she stop treatment. She experienced 2 more episodes of hearing loss in the 1st and 3rd treatment cycle and was treated as an outpatient. In the follow-up she had lasting tinnitus which was considered a consequence of the hearing loss. (No causal relationship)
13. After 7 months of treatment, a 32 year old subject had an enlarged cervical lymph node for 5 weeks. She was hospitalized for 12 days for excision of the lymph node. Histology showed a "chronic

partially phlegmonous infection with advanced scarring". The study drug was continued. (Causal relationship unlikely)

14. A 24 year old subject underwent an appendectomy after 1 year of study medication. Treatment was not interrupted. (No causal relationship)
15. A 32 year old subject underwent a laparoscopic gastroplasty for a hiatus hernia. Study medication had been taken for 4 months and was not stopped. (No causal relationship)
16. A 24 year old subject underwent an osteotomy of a metatarsal bone for pain and inflammation 4 days before the start of medication. 6 months later a postoperative inflammation made removal of 2 pins under general anesthesia necessary. Treatment was not interrupted. (No causal relationship)
17. A 31 year old underwent surgery for an anal fissure caused by a hemorrhoidal infection after more than 1 year of treatment. (No causal relationship)
18. A 25 year old was hospitalized for appendicitis in the follow-up period after 2 years of treatment. She underwent an appendectomy. (No causal relationship)
19. A 26 year old subject underwent a laparoscopic appendectomy for appendicitis after 9.5 months of treatment. Treatment was not interrupted. (No causal relationship)
20. Another 25 year old subject underwent appendectomy for appendicitis after approximately 2 years of treatment. Treatment was not interrupted. (No causal relationship)
21. A 26 year old was diagnosed with an ovarian cyst before the start of the trial. One month later, a laparoscopy was performed and the cyst punctured. Cytology was benign. After 6 months of treatment, the right ovary was exstirpated due to enlargement of the cyst. Histology showed a benign mucinous cystadenoma. Treatment was not interrupted. (No causal relationship)

Serious adverse events in Marvelon® users included

1. Pap III
2. Abrasio for cervical polyp and laparoscopic sterilization in follow-up
3. Surgery for relapse of Crohn's disease
4. Fibroadenoma of left breast
5. Anorexia nervosa requiring hospitalization
6. Appendectomy
7. Car accident with fracture of the sternum
8. Resection of ethmoid septum for chronic sinusitis
9. Bilateral breast reduction for hypertrophy of breast
10. Tonsillectomy
11. Arthroscopy of shoulder
12. Appendectomy
13. Appendectomy after hospitalization for suspected pelvic inflammatory disease
14. Visual impairment due to atrophic scar on fovea
15. Herniated intervertebral discs

48 (11%) of Yasmin™ users and 42 (9%) of Marvelon® users discontinued treatment because of adverse events. The most common AEs leading to discontinuation were intracyclic bleeding (1.6% of Yasmin™ subjects and 0.9% of Marvelon® users) and dysmenorrhea (1.1% of Yasmin™ users and 1.8% of Marvelon® users). All other AEs leading to discontinuation occurred in <1% of subjects. For Yasmin™ users, these AEs include weight gain in 2 subjects, PMS in 5 subjects, breast pain in 5 subjects, depression in 2 subjects, emotional lability in 1 subject, headache in 4 subjects and migraine in 2 subjects, peripheral vascular disorder in 1 subject, suspected pulmonary embolus in 1 subject (SAE described above).

9 Yasmin™ users (2%) vs. 15 Marvelon® users (3.4%) reported acne as an adverse event.

One Yasmin™ user was diagnosed with diabetes near the end of the study. She discontinued after the 23rd cycle and started treatment with Glucophage.

Peripheral vascular disorder was listed as an adverse event for 4 Yasmin™ users but is not further described. One other Yasmin™ user reported thrombophlebitis as a non-serious adverse event, and no further details are provided.

Laboratory parameters
Reviewer's comment

- **The information presented below describes Yasmin™ subjects**
- **Many serum samples were noted to be hemolyzed, incompletely separated, or whole blood. A large number of values are reported that are not compatible with human life, including multiple potassium values as high as 15, many of them from baseline sampling. This leads to concern about the reliability of the following data.**

Liver parameters
Four Yasmin™ subjects and two Marvelon® subjects had elevated liver parameters at some time during the study but which resolved on repeat measurements.

One subject had significantly elevated values at baseline, alkaline phosphatase 186 U/L (normal range 60-170), GGT 30 U/L (normal 0-18), ASAT/GOT 71 U/L (normal 0-18), ALAT/GPT 94 U/L (normal 0-17), LDH 482 U/L (normal 0-240), and bilirubin 1.0 mg/dl (normal 0-1.0) She received the study drug, and all values had returned to normal at visit 3.

Alkaline phosphatase (normal range 60-170 U/L): 5 subjects changed from normal at baseline to a high value and 12 changed from high at baseline to normal. The maximum value at screen was 285 U/L, and the maximum value at end of study was 271 U/L. Median change from screen to end of study was a decrease of 19 U/L, with a range from a decrease of 218 U/L to an increase of 141 U/L. No subject had a value 3 times the upper limit of normal (3 x ULN).

Gamma-GT (normal 0-18 U/L): 20 subjects changed from normal at baseline to a high value, and 6 changed from high at baseline to a normal value. The maximum value at screen was 185 U/L, and the maximum at end of study was 150 U/L. The median change from baseline to end of study was 0, with a range from a decrease of 35 U/L to an increase of 65 U/L.

One Yasmin™ subject had persistently high GGT and underwent a cholecystectomy (GGT values were 185,125,140,150 U/L at visits 1, 3, 6, and end of study, respectively). Another had moderately elevated GGT values (43, 43, 39, 32 U/L).

ASAT/GOT (normal range 0-18 U/L): 4 subjects changed from normal at baseline to a high value, and 4 changed from a high value at baseline to normal. The maximum value at screen was 71 U/L, and the maximum value at the end of the study was 22 U/L. The median change from screen to end of study was 0, ranging from a decrease of 58 U/L to an increase of 13 U/L. No subject had a value after the baseline value that was 3 x ULN.

ALAT/GPT (normal range 0-17 U/L): 21 subjects changed from normal at screen to a high value, and 7 changed from a high value at screen to normal. The maximum value at screen was 94 U/L and at end of study was 125 U/L. The median change from baseline to end of study was 0, ranging from a decrease of 83 U/L to an increase of 113 U/L.

One subject had normal liver function values until the end of the study, when her GGT was elevated to 74 (>3 x ULN), ALAT/GPT was 125 (>3 x ULN), and bilirubin remained normal at 0.4 mg/dl). She completed all 26 cycles with no adverse events. There were no AEs reported at follow-up, and no further information is provided.

Bilirubin (normal range 0-1 mg/dl): 8 subjects changed from normal at baseline to a high value, and 5 changed from a high value at screen to normal. The maximum value at baseline was 1.60 mg/dl, and the

maximum at the end of the study was 1.20 mg/dl. The median change from baseline to the end of the study was 0, ranging from a decrease of 0.7 mg/dl to an increase of 0.5 mg/dl. No subject had a value 3 x ULN.

Electrolytes

Sodium (normal range 135-153 mmol/l): 4 subjects changed from a low value at baseline to normal, 2 from normal to high and 5 from normal to low. The range at baseline was 128 to 150 and at the end of the study 134 to 170. The median change from baseline to the end of the study was a decrease of 1, ranging from a decrease of 11 to an increase of 28.

One Yasmin™ subject had sodium values of 142, 143, 139, and 170 mmol/l at visits 1, 3, 6, and the end of the study, respectively. Her chloride values were 101, 104, 102, and 89 mmol/l (normal range 94-111). Her potassium was also noted to be high at 6.0 mmol/l at the end of the study, with a notation that the serum sample was whole blood. The only adverse events reported were breast pain at visit 3, cystitis and accidental injury at visit 7 (the final visit). No AEs were reported at follow-up. She was noted to be pregnant with a last menstrual period of September 11, 1995. The last study medication was July 26, 1995.

Potassium (normal range 3.5-5.3mmol/l): 1 subject changed from low to normal, 79 from normal to high, 35 from high to normal, and 1 from normal to low. The range at baseline was 3.2 to 15.0 mmol/l and at the end of the study 3.6 to 15.0 mmol/l. The median change from baseline to the end of the study was an increase of 0.1 mmol/l, ranging from a decrease of 9.9 mmol/l to an increase of 10.7 mmol/l.

One Yasmin™ subject (416) was treated with spironolactone for breast tension during the study. Potassium levels were not determined near the time of treatment. All of her routine potassium values during the study were normal.

Reviewer's comment

For both Yasmin™ and Marvelon® subjects, numerous specimens were noted to be "hemolyzed" or "incompletely separated" or "whole blood". The values varied widely within individuals, and some values both at baseline and during treatment were too high to be compatible with life. Therefore, no meaningful conclusions can be drawn from this data, as it is unreliable.

Chloride (normal range 94-111 mmol/l): 2 subjects changed from low values at baseline to normal, 4 from normal to low, 1 from normal to high, and 7 from high to normal. The range at baseline was 89-114 mmol/l, and at the end of the study 89-107 mmol/l. The median change from baseline to the end of the study was a decrease of 3 mmol/l, ranging from a decrease of 14 mmol/l to an increase of 7 mmol/l.

Renal parameters

BUN (normal range 0-23 mg/dl): 1 subject changed from normal at baseline to a high value, and 1 changed from a high value to normal. The maximum value at baseline was 26 mg/dl, and the maximum at the end of the study was 23 mg/dl. The median change from baseline to the end of the study was 0, ranging from a decline of 13 mg/dl to an increase of 9 mg/dl. There were no clinically significant values.

Creatinine (normal range 0-1.2 mg/dl): 41 subjects changed from normal at baseline to a high value. 6 changed from a high value to normal. The maximum value at baseline was 1.34 mg/dl, and the maximum at the end of the study was 1.39 mg/dl. The median change from baseline to the end of the study was an increase of 0.09 mg/dl, ranging from a decline of 0.43 mg/dl to an increase of 0.57 mg/dl. There were no clinically significant values.

Uric acid (normal range 2.4-5.7 mg/dl): 44 subjects changed from normal at baseline to a high value, and 16 changed from high at baseline to normal. The range at baseline was 2.1-7.1 mg/dl, and at the end of the study 1.9-6.7 mg/dl. The median change from baseline to the end of the study was a decrease of 0.3 mg/dl, ranging from a decrease of 2.9 mg/dl to an increase of 3.4 mg/dl. There were no clinically significant values.

Other chemistry parameters

LDH (normal range 0-240 U/L): 24 subjects changed from normal at baseline to a high value at the end of the study, and 15 changed from a high value at screen to normal. The maximum value at screen was 1350 U/L, and the maximum value at the end of the study was 615 U/L. All of the significantly elevated values were from serum samples that were noted to be whole blood or hemolyzed. The median change from baseline to the end of the study was a decrease of 2.0 U/L, ranging from a decrease of 325 U/L to an increase of 437 U/L. No subject had a value after the baseline that was 3 x ULN.

Cholinesterase (normal range 2.8-7.4 kU/L): 3 subjects changed from a low value at baseline to normal, 4 changed from normal at baseline to low, 2 changed from normal to high values, and 5 changed from high at baseline to normal. Values at baseline ranged from 2.3 to 8.0 kU/L, and at the end of the study 2.1 to 6.7 kU/L. The median change from baseline to end of study was a decline of 0.6 kU/L, ranging from a decline of 3.2 kU/L to an increase of 2.3 kU/L.

Alpha amylase (normal range 0-120 U/L): 8 subjects changed from normal at baseline to a high value, and 2 changed from a high value at baseline to normal. The maximum value at baseline was 167 U/L, and the maximum at the end of the study was 187 U/L. The median change from baseline to the end of the study was a decline of 4.0 U/L, ranging from a decline of 50 U/L to an increase of 59 U/L.

Calcium (normal range 2.02-2.60 mmol/l): 16 subjects changed from normal at baseline to a high value, 1 from normal to low, and 8 from high to normal. The range at baseline was 2.20-2.87 mmol/l and at the end of the study 1.76 to 2.88 mmol/l. The median change from baseline to the end of the study was a decrease of 0.05 mmol/l, ranging form a decrease of 0.83 mmol/l to an increase of 0.18 mmol/l.

Inorganic Phosphate (normal range 0.87 to 1.45 mmol/l): 17 subjects changed from low at baseline to normal and 3 from low to high. 38 changed from normal to low and 75 from normal to high. 45 changed from high to normal and 4 from high to low. The range at baseline was 0.67 to 6.99 mmol/l and at the end of the study 0.52 to 8.08 mmol/l, and the range was similar in the Marvelon® group. Numerous subjects had isolated values that were markedly elevated, some at baseline, and some during treatment. The median change from baseline to the end of the study was a decrease of 0.02 mmol/l, ranging from a decrease of 5.45 mmol/l to an increase of 6.77 mmol/l.

Total protein (normal range 66-87 g/l): 13 subjects changed from a low value at baseline to normal, 26 changed from normal to low and 2 from high to normal. The range at baseline was 61-89 g/l and at the end of the study 60-83 g/l. The median change from baseline to the end of the study was a decrease of 2 g/l, ranging from a decrease of 14 g/l to an increase of 12 g/l.

Albumin (normal range 55-70%): 10 subjects changed from a low value at baseline to normal, 11 from normal to low, 3 from normal to high and 1 from high to normal. The range at baseline was 53.2 to 70.9%, and at the end of the study 48.8 to 71.8%. The median change from baseline to the end of the study was a decrease of 0.1%, ranging from a decrease of 13.6% to an increase of 12.9%.

Alpha-1-globulin (normal range 2.0-5.0%): 2 subjects changed form a low value at baseline to normal at the end of the study, 2 from normal to low, 34 from normal to high, and 8 from high to normal. The range at baseline was 1.8 to 6.1% and at the end of the study 0.4 to 5.9%. The median change from baseline to the end of the study was an increase of 0.1%, ranging from a decrease of 3.6% to an increase of 2.9%.

Alpha-2-globulin (normal range 5.0-10.0%): 82 subjects changed from normal at baseline to a high value at the end of the study, 1 from normal to low and 30 from high to normal. The range at baseline was 5.3 to 14.3% and at the end of the study 5.6 to 13.4%. The median change from baseline to the end of the study was an increase of 0.2%, ranging from a decrease of 5.7% to an increase of 4.9%.

Beta-globulin (normal range 10.0-15.0%): 108 subjects changed from a low value at baseline to normal, 79 from normal to low, and 6 from normal to high. The range at baseline was 6.9 to 18.3% and at the end of

the study 7.8 to 20.3%. The median change from baseline to the end of the study was an increase of 0.5%, ranging from a decrease of 4.2% to an increase of 10.2%.

Gamma-globulin (normal range 12.0-20.0%): 33 subjects changed from a low value at baseline to normal at the end of the study, 56 from normal to low, 11 from normal to high and 5 from high to normal. The range at baseline was 9.1 to 21.6% and at the end of the study 7.4 to 22.9%. The median change from baseline to the end of the study was a decrease of 0.6%, ranging from a decrease of 6.9% to an increase of 6.7%.

Hematology parameters

Hemoglobin (normal range 12.0-16.0 g/dl): 10 subjects changed from a low value at baseline to normal and 39 changed from normal to low. The minimum value at baseline was 10.2 g/dl and at the end of the study 10.4 g/dl. The median change from baseline to the end of the study was a decrease of 0.1 g/dl, ranging from a decrease of 3.6 g/dl to an increase of 3.1 g/dl.

Hematocrit (normal range 37-47%): 51 subjects changed from normal at baseline to low, and 14 changed from low at baseline to normal, and 17 changed from normal to high. The minimum value at baseline was 32% and at the end of the study 31%. The median change from baseline to the end of the study was a decrease of 1.0%, ranging from a decrease of 11% to an increase of 10%.

Fibrinogen (normal range 150-450 mg/dl): 2 subjects changed from a low value at baseline to normal, 4 changed form normal to low, 16 from normal to high, and 5 from high to normal. The range at baseline was 108-593 mg/dl, and at the end of the study 153-608 mg/dl. The median change from baseline to the end of the study was a decrease of 5.0 mg/dl, ranging from a decrease of 182 mg/dl to an increase of 315 mg/dl.

WBC (normal range 3.8-9.0/nl): 11 subjects changed from a low value at baseline to normal, 16 changed from normal to low, and 34 changed from normal to high, and 21 changed from high to normal. The range of values at baseline was 2.6 to 15.1/nl and at the end of the study 1.7 to 15.0/nl. The median change from baseline to the end of the study was a decrease of 0.1/nl, ranging from a decrease of 11.4/nl to an increase of 8.5/nl.

One Yasmin™ subject had WBC values of 7.5 and 7.3/nl at visits 1 and 3, respectively, and a very low value of 1.7 at the end of the study. She finished 26 cycles. The adverse events reported during the study were pruritis, rash, headaches, eczema, tinnitus, and at the final visit an unspecified circulatory disorder and leukopenia. There were no adverse events reported at follow-up.

Platelets (normal range 150-450/nl): 7 subjects changed from a low value at baseline to normal, 14 from normal to low, and 6 from high to normal. The range at baseline was 72-525/nl, and at the end of the study 65-445/nl. The median change from baseline to the end of the study was an increase of 5/nl, with a range from a decrease of 257/nl to an increase of 178/nl. One subject entered the study with a low platelet count which persisted (85, 55, 60, 65 per nl at visits 1, 3, 6, and end of study). The investigator considered her to have idiopathic thrombocytopenia.

Cervical cytology

At baseline 59.5% of subjects had CI Pap results, 28.5% had CII, and 12% did not have a Pap performed. At the end of the study 49.5% had CI, 33.9% CII, 1% CIII, and 15.6% did not have a Pap performed. 39 subjects changed from CI at baseline to CII at the end of the study, and 1 changed from CI to CIII. 23 subjects changed from CII to CI, and 3 from CII to CIII.

Reviewer's comment

Given that cervical dysplasia is not an uncommon finding among sexually active women and that the false-negative rate for a single Pap test (e.g., the cytology result at screen) is 10-25%, these findings do not suggest an effect of Yasmin™ on cervical cytology.

Blood pressure
Systolic blood pressure ranged from 90 to 153 mm Hg at baseline and 80 to 158 at the end of the study. Diastolic blood pressure ranged from 55 to 100 at baseline and 50 to 100 at the end of the study. Heart rate ranged from 56 to 120 at baseline and 54-114 at the end of the study. No clinically significant changes in mean systolic or diastolic blood pressures or heart rate were observed, although individual women had sporadic abnormal measurements.

Hypertension was reported as an adverse event for 2 Yasmin™ users and 1 Marvelon® user. One Yasmin™ user was treated for hypotension.

Weight change
Weight gain was reported as an adverse event in 5 (1.1%) Yasmin™ users and 3 (0.7%) Marvelon® users. Weight change with Yasmin™ ranged from 27 kg lost (at cycle 16) to 13 kg gained (at cycle 20). The median weight change at cycle 26 was a gain of 0.3 kg ranging from 23.5 kg lost to 10.8 kg gained. At cycle 26, 19% of subjects had lost more that 2 kg, and 25% had gained more than 2 kg. Weight change with Marvelon® ranged from 16 kg lost (at cycle 23) to 14.5 kg gained (at cycle 22). The median weight change from baseline to cycle 26 was a gain of 0.8 kg, ranging from 14 kg lost to 14 kg gained. At cycle 26, 17% of Marvelon® subjects had lost more than 2 kg and 30% had gained more than 2 kg.

Reviewer's comment
Despite the antimineralocorticoid effect of DRSP, weight change is comparable between treatment groups. Whereas this was an open label trial and the women recorded their own weights, no comparative claims could be made regarding weight change. In addition, one Yasmin™ subject took Fenfluramine for weight control during the study.

PMS
17% of Yasmin™ users and 15% of Marvelon® users reported symptoms of PMS in the 6 months before the study. 18% of Yasmin™ users and 20% of Marvelon® users reported symptoms during the study. PMS was the second most frequently reported AE during this study in both treatment groups.

Allergic reactions
No anaphylactic reactions were reported in Yasmin™ users vs. 1 Marvelon® user.

4.0 CLINICAL STUDY 96049B (Report No. 98180): U.S. "Pivotal" Phase 3 Efficacy and Safety Study

4.1 Title

An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 30 µg

4.2 Study objective

The primary objective of this study was to evaluate the contraceptive efficacy and safety of DRSP 3mg/ EE 30 µg (Yasmin™) tablets. The secondary objective was to evaluate the effects of the Yasmin™ tablets on the menstrual cycle.

4.3 Study design

Phase 3, single group, open-label, multicenter efficacy and safety study of 300 healthy women at risk of becoming pregnant, conducted at 6 study centers in the US. Each woman received Yasmin™ for 21 days, followed by a 7 days of placebo tablets for a treatment period of 13 cycles (12 months).

4.4 Study population

333 healthy women of childbearing age were enrolled. 7 subjects took no study drug. Therefore, all assessments are based on 326 subjects. 220 subjects (68%) completed all 13 treatment cycles. Regardless of completing the study, 237 subjects (73%) of the 326 evaluated had a 2-week follow-up visit.

All participants were 18 to 35 years old, were at risk of becoming pregnant, and were willing to use an oral contraceptive. Subjects must have had regular cycles of menstrual or withdrawal bleeding for the 3 month period preceding enrollment, and the menstrual cycle must have been between 21 and 35 days, inclusive. Subjects who were postabortal or postpartum must have had 3 consecutive normal menstrual cycles. All subjects were required to have a negative pregnancy test within two weeks prior to the first dose of study drug and to have signed a written informed consent immediately preceding treatment. Efforts were made in the recruitment phase to achieve a balance between new OC users (starters) and subjects who had previously used OCs (switchers).

87% of the subjects were Caucasian. The mean age was 26.4 years, with a range of 18 to 35 years. 13% of subjects were current smokers, and the mean number of cigarettes/day for the smokers was 5.5 $\pm$ 3.3, with a range of 1 to 10. 36% of subjects had a history of mild dysmenorrhea, 11% moderate dysmenorrhea, and 4% severe dysmenorrhea. 46% of subjects were new users of OCs (had not used OCs in the month prior to study participation) and 54% were switchers. 53% had at least 1 previous pregnancy.

4.5 Inclusion and exclusion criteria

Inclusion criteria

1. Healthy females of reproductive age, 18 to 35 years, within 25% of ideal body weight (according to Metropolitan Life Tables), who were at risk of becoming pregnant and were willing to use an oral contraceptive
2. Previous OC users and nonusers; women currently using OCs could be enrolled directly (with no washout cycle)
3. Subjects having regular menstrual cycles for the 3-month period preceding enrollment. Menstrual cycle length must be between 21 and 35 days
4. Subjects who were postabortal or postpartum having had 3 consecutive normal menstrual cycles immediately preceding treatment
5. All subjects had to have a negative pregnancy test within 2 weeks prior to the first dose of study drug.
6. In the opinion of the investigator, the subject was expected to be compliant with the protocol during the course of the study.
7. Subjects had to have signed an informed consent.

Exclusion criteria

1. Smoked more than 10 cigarettes per day
2. Was over 30 years old and currently smoking
3. Used injectable estrogens, progestogens, or androgens during the 3-month period prior to enrollment
4. Used a contraceptive implant within 6 months prior to enrollment
5. Intention of using other methods of contraception during the study, in addition to or in lieu of study drug, or whose partner(s) use condoms to prevent transmission of sexually transmitted diseases or AIDS
6. A desire for pregnancy or nursing
7. Diabetes mellitus or known to have had an abnormal glucose tolerance test during pregnancy
8. A systolic blood pressure of >140 mm Hg or a diastolic blood pressure of >90 mm Hg (in the sitting position) or currently receiving any treatment for hypertension
9. Abnormal baseline laboratory values that are considered clinically significant and which suggest specific organ dysfunction

10. A contraindication for the use of oral contraceptives, including any of the following:
    - Thrombophlebitis or thromboembolic disorders
    - Known or suspected clotting disorders
    - Cerebral vascular or coronary artery disease
    - Known or suspected carcinoma of the breast
    - Known or suspected estrogen-dependent neoplasia
    - Genital bleeding of unknown cause
    - Known or suspected pregnancy
    - Benign or malignant liver tumor
    - Pituitary tumor
    - Cholestatic jaundice of pregnancy or jaundice with prior oral contraceptive use
11. A history of migraine, increased frequency or severity of headaches during previous estrogen or oral contraceptive therapy
12. A history of allergy to any of the study drugs or related drugs
13. A history of porphyria
14. A history of middle ear deafness with deterioration in a previous pregnancy
15. Eruption of blisters during a previous pregnancy (herpes of pregnancy)
16. A history of disorders of lipid metabolism
17. Evidence of active heart, lung, kidney, liver, endocrinological, neurological, psychiatric, gastrointestinal disease, or malignancy
18. A positive gonorrhea test
19. A positive chlamydia culture or antigen test
20. A history of, or current alcohol or drug abuse
21. Current cervical cytologic smear with evidence of squamous intraepithelial lesion
22. Received or are receiving Tegison® tablets (etretinate) within 4 months, Accutane® tablets (isotretinoin) within 30 days, oral tetracycline therapy within the last 10 days prior to enrollment, or currently receiving phenobarbital, phenytoin, or rifampin
23. Participation in another clinical study of an investigational drug within the last 3 months

4.6 Screening period

Baseline evaluations included medical, surgical, and gynecological history, medication history, physical examination (including breast and pelvic examinations), vital signs (including weight, temperature, blood pressure, and pulse rate), Pap smear, Gonorrheal probe, Chlamydia Trachomatis culture or antigen test, blood chemistry (after a 12-hour fast), hematology, and urinalysis tests, T3 and T4, and β-HCG pregnancy test. Study drug and subject diary were dispensed, and the Menstrual Distress Questionnaire (MDQ) was administered.

4.7 Treatment period

Upon satisfactory completion of all baseline clinical and laboratory evaluations, each subject was given enough study drug (Yasmin™) for one 28-day cycle. At the end of Cycle 1, enough Yasmin™ for Cycles 2 and 3 was dispensed. At the end of Cycles 3 and 6, enough Yasmin™ was dispensed for 3 cycles, and at the end of Cycle 9, Yasmin™ was dispensed for 4 cycles. At each visit, all previously dispensed blister packs were to be returned to the investigator even if they still contained unused tablets.

Subjects were instructed to take their first tablet on the first day of their menstrual cycle or withdrawal bleeding. To achieve maximum contraceptive effectiveness, tablets had to be taken exactly as directed and at intervals not exceeding 24 hours. Tablets were taken without interruption for 28 consecutive days.

After all 28 tablets from the first package were taken, the first tablet from the next package was taken the next day and the 28-day dosing schedule was continued. The start day had to be the same for each package for all cycles.

If the woman started taking the tablets later than the first day of her menstrual cycle, she was instructed to use an additional nonhormonal (barrier) method of contraception until she had taken tablets for 7 consecutive days.

Each subject was expected to receive Yasmin™ for a treatment period of 13 cycles (12 months).

A complete physical examination including pelvic exam, cervical cytology, and breast exam was performed after the end of Cycles 6 and 13 or Final Visit. Vital signs including weight, temperature, blood pressure, and pulse rate were obtained at each visit. All concomitant medications were documented at baseline and all subsequent visits. All adverse events were document at all visits whether or not they were considered drug related. Blood chemistry (after a 12-hour fast), hematology and urinalysis were repeated at Cycles 6 and 13 or Final Visit. β-HCG pregnancy tests were performed at Cycle 13 or the Final Visit or at additional visits as deemed necessary by the investigator.

Subjects filled in diary cards supplied by the Sponsor to record the days tablets were taken or omitted, menses and intermenstrual bleeding, whether the bleeding was light, normal or heavy, and comments.

Each subject was to undergo evaluations for efficacy and safety at the end of cycles 1, 3, 6, 9, and 13. Post-study visits were scheduled at 3 months, and if necessary at 6 and 12 months. If a subject discontinued prematurely, every attempt was to be made to complete the evaluations that would have been performed at the final visit. Subjects in whom pregnancy had not been ruled out at the completion of the study were to be seen approximately 2 weeks after the final visit.

All subjects were to be followed for a minimum of 3 months when they discontinued the study. A visit was to be scheduled 3 months after discontinuation to determine the subject's general health status, and if any clinically significant events, including pregnancies, had occurred. A serum pregnancy test was to be performed. Additional contacts were to be scheduled at 6 and 12 months if necessary to determine the outcome of pregnancies and serious adverse events. Information on pregnancy and outcome were collected on all subjects becoming pregnant during the study or within 1 cycle of withdrawing from the study. Subjects who were amenorrheic when they left the study were to be followed for 3 months or longer if clinically indicated until return of menses.

4.8 Statistical Procedures

The primary efficacy variable was the pregnancy rate. Pregnancy tests were scheduled at baseline, Cycle 13 or Final Visit. The Pearl Index and Life table methods were used to assess the pregnancy rate. Cycles in which nonhormonal (barrier) methods were used were deleted from the computation of the Pearl Index, while all subsequent cycles were also deleted for the life table method.

Secondary efficacy variables were measures of cycle control and intermenstrual bleeding. Cycle control was characterized by cycle length, length of menses, and the number of days with breakthrough bleeding or spotting. These parameters were determined from the subjects' diaries. Descriptive statistics were provided for cycle length, length of menses, and the proportion of cycles without breakthrough bleeding or spotting.

Intermenstrual bleeding was summarized by duration and type. Bleeding which was not withdrawal bleeding and described as light bleeding in the subject's diary was considered as spotting. Normal or heavy bleeding that is not withdrawal bleeding was considered as breakthrough bleeding. The following parameters were calculated for intermenstrual bleeding:

- Crude incidence rate: The proportion of subjects in whom the event occurred at least once during the entire study
- Cumulative incidence rate (Life Table Method) by cycle: the proportion of women in whom the event occurred at least once from the beginning of the study to the end of each of the successive cycles
- Incidence rate by cycle: the proportion of women in whom the event occurred at least once within a particular cycle

- Total frequency of events: the frequency of the event occurring in a woman during the entire study
- Frequency of event by cycle: the frequency of the event occurring in a woman within a particular cycle.

No formal methods were used to calculate sample size. Approximately 300 women were expected to be enrolled. Each woman was expected to receive Yasmin™ for a minimum treatment period of 13 cycles (12 months). The dropout rate was anticipated to be approximately 2% per month, with approximately 240 women completing at least 13 cycles.

The primary analysis was based on intent-to-treat. A subgroup analysis was performed for subjects who did not miss any tablets.

Summary statistics were presented for the treatment means and for mean changes from baseline. A paired t-test was used to test mean changes from baseline.

4.9 Evaluation Criteria

The primary efficacy variable, contraceptive efficacy, was assessed by the Pearl Index (pregnancy rate per 100 woman-years), and pregnancy ratio (the percent of women completing the study without any additional contraception who became pregnant during the study). The secondary efficacy variable was cycle control, which was assessed by evaluation of the characteristics of the withdrawal bleeding pattern and intermenstrual bleeding; i.e., breakthrough bleeding and/or spotting.

Safety was assessed from the following parameters: Treatment duration, vital signs, physical and pelvic exams, Pap smears, laboratory tests, and adverse events.

4.10 Withdrawals and compliance

Subjects had the right to withdraw from the study at any time. Whenever possible, reasons for discontinuation were reported and a complete final examination, including physical examination and clinical tests, were performed at the time of withdrawal. Subjects were to be withdrawn for the following reasons:

1. Occurrence for the first time of migraine headaches or more frequent occurrence of unusually severe headaches
2. Sudden perceptual disorders (e.g., disturbances of vision or hearing)
3. First signs of thrombophlebitis or thromboembolic symptoms (e.g., unusual pain in or swelling of the legs, stabbing pains, pain when breathing, or coughing for no apparent reason)
4. A feeling of pain and tightness in the chest
5. Pending operations (6 weeks beforehand)
6. Immobilization (e.g., following accidents)
7. Onset of jaundice
8. Onset of hepatitis
9. Itching of the whole body
10. Epileptic seizures
11. Significant (per the investigator's discretion) rise in blood pressure

Premature Discontinuations	
Reason	Number (%) of Subjects
Adverse Event	20 (6)
Lack of Efficacy	1 (<1)
Protocol Deviation	18 (6)
Withdrawal of Consent	26 (8)
Other	38 (12)
Missing Information	3 (<1)
Total discontinuations	106 (32)

The most common "other" reasons were "lost to follow-up" (27 subjects/8%) and noncompliance to study regimen (2 subjects), and relocation of subjects (9 subjects).

Over 72% of subjects missed no study drug pills during the study. Total compliance per cycle varied between 87% and 92%. 8% to 13% of subjects missed more than 3 pills in any cycle, including subjects who discontinued pill intake during that cycle.

A total of 7 subjects (2% of 308 subjects with data) used other contraceptive methods at least once during the study. One used a condom in Cycle 1. 3 subjects used condoms in Cycles 2 and 3. One used a barrier and spermicide in Cycle 7 through Cycle 9. One subject went back to her prior birth control pill, and one did not identify the alternate contraception.

Concomitant medication was taken by 66% of the subjects at some time during the study, mostly anti-inflammatory agents, analgesics, antibiotics, antihistamines, and antitussives.

4.11 Efficacy analysis

One pregnancy occurred during the study. The corrected Pearl Index (based on 1 pregnancy in 3,192 cycles, of 326 subjects, in which no alternative methods of contraception were used) was 0.407, and the uncorrected Pearl Index was 0.406. The pregnancy ratio was 0.455, both uncorrected and corrected.

The one pregnancy occurred in a 30-year-old parous Caucasian woman, an OC switcher. She missed her period after Cycle 3 due to pregnancy. On Day 5 of Cycle 3 she missed 1 tablet and took 2 tablets the following day. The subject discontinued the study and had an abortion 4 weeks after conception.

A pregnancy occurred after discontinuation in a 29-year-old, parous Caucasian woman who was an OC switcher. She discontinued the study drug on Day 21 of Cycle 1 and conceived during the second cycle following discontinuation of the study. She was not counted as a contraceptive failure due to the fact that she became pregnant after she discontinued the study drug.

Formal Life Table methods were not applied to the evaluation of pregnancy rate as specified in the protocol because the number of pregnancies was low. The number of pregnancies observed, divided by the number of 13-cycle completers without use of alternative means of contraception is equivalent to an upper bound of the life-table failure rate.

Reviewer's comment:
54 subjects are identified who did not have a final pregnancy test upon completion or discontinuation from the study. Therefore, no conclusions can be made regarding efficacy of the study drug in those subjects. 5 of these had a follow-up at 2 weeks and one more had a follow-up at 3 months. They were presumed not to be pregnant because they had resumed menstrual bleeding.

The median cycle length for all subjects in Cycles 2 through 13 was 28 days. The median cycle length in the first cycle was 23 days, a result of starting pill intake on the first day of the previous menstrual or withdrawal bleeding. Cycle length was between 26 and 30 days in 87% of subjects in Cycle 2 and increased to 94% of subjects in Cycle 12.

The median duration of withdrawal bleeding for all subjects was 5 days in Cycles 1 through 12, and 4 days in Cycle 13. The duration of withdrawal bleeding was 4 to 7 days for 71% to 83% of subjects during the study. A duration of 1 to 3 days of withdrawal bleeding was seen in 13 to 26% of subjects, and >7 days in 0 to 5%. Results for switchers and new users were similar, except for a longer duration of bleeding in Cycle 1 for new users (>7 days in 8% of new users compared to 4% of switchers).

63% to 72% of subjects for each cycle described the intensity of withdrawal bleeding as normal. 14% to 20% of subjects described it as light, and 11% to 20% described it as heavy. Bleeding intensity did not significantly change among cycles.

Amenorrhea, or the absence of withdrawal bleeding, occurred at some time during the study in 21% of subjects. 16% of subjects had only 1 episode of amenorrhea, 2% had 2 episodes, and 3% had more than 2 episodes. It was seen in 5% of subjects at the end of Cycle 1 and varied from 1% to 5% of subjects per cycle thereafter. Amenorrhea in Cycle 1 was more common in new users (6%) than in switchers (4%).

49% of subjects reported no intermenstrual bleeding during any cycle. Breakthrough bleeding without spotting occurred in 1% of all cycles, in 2% of subjects during at least 1 cycle, and in 0.3% to 2% of all subjects per cycle. Spotting without breakthrough bleeding occurred in 30% of subjects during at least 1 cycle, varying from a maximum of 20% of all subjects in the first treatment cycle to a minimum of 5% in Cycle 7. Both breakthrough bleeding and spotting occurred in 1% to 4% of subjects during the study, and in 19% of all cycles. Of the 151 subjects with intermenstrual bleeding at any time during the study, 64% had intermenstrual bleeding during only 1 or 2 pill cycles.

4.12 Safety analysis

Deaths

There were no deaths during the study.

Adverse events

71% of subjects reported at least 1 AE during the study. One subject reported a serious AE, unrelated to the study drug (breast augmentation surgery). 20 subjects (6%) discontinued because of AEs. The most frequently reported AEs leading to discontinuation were

emotional lability	5 (1.5%)
headache	5 (1.5%)
nausea	4 (1.2%)
dysmenorrhea	2 (0.6%)
intermenstrual bleeding	2 (0.6%)
depression	2 (0.6%)

Other AEs resulting in subject discontinuation (1 subject each, 0.3%) were breast engorgement, breast pain, increased appetite, weight gain, enlarged abdomen, hyperthyroidism, dry eye, accident, nervousness, and impaired concentration. 7 subjects were discontinued for 2 or more different AEs.

The following AEs classified as related to the study drug were reported in ≥ 1 % of subjects (N=326)

breast pain	28 (9%)	acne	7 (2%)
headache	16 (5%)	Abdominal enlargement	6 (2%)
emotional lability	13 (4%)	Weight gain	5 (1%)
dysmenorrhea	8 (2%)	Intermenstrual bleeding	5 (1%)
nausea	8 (2%)	Vaginal moniliasis	5 (1%)

Convulsions were reported by one subject. This 31yo white woman entered the study with a past history of seizures and was on no anti-convulsant medications. Convulsions were reported as an adverse event at the