CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-098

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies[1]

NDA:	21-098
Applicant:	Berlex
Name of drug:	Yasmin 21/28 Tablets (drospirenone 3 mg and ethinyl estradiol 0.030 mg tablets)
Indication:	Prevention of pregnancy
Documents reviewed:	Amendment dated November 6, 2000, "Complete Response to July 10, 2000 Approvable Letter"; "Response to clinical information request letter of February 2, 2001", dated March 9, 2001
Medical reviewer:	Scott Monroe, M.D. (HFD-580)

This statistical review evaluates results of serum potassium data from two studies that were not in the original NDA.

My review concludes the data submitted are insufficient to conclude drospirenone 3 mg and ethinyl estradiol 30μg does not affect serum potassium levels. The studies were not prospectively designed to assess this relationship; serum potassium levels were measured infrequently.

Review:

Study 1
The medical reviewer believes the information contained in a premeeting document from September 2000 is pertinent to the assessment of hyperkalemia. Therefore, he requested the applicant to submit certain information to this NDA. Serum potassium was measured at baseline, 6 months, and 12 months.

Although there appears to be a dose response between dose and change from baseline, these changes are not clinically important. This relationship is expected because of the pharmacology of drospirenone.

The numbers of patients contained in the submitted datasets do not exactly agree with the reported numbers. The reported numbers are each greater than those in the datasets, ranging from an increase of one to an increase of five. However, the reported summary statistics and the summary statistics I calculated from the datasets are essentially identical.

[1] Keywords: Safety

The study was designed to evaluate the safety and efficacy of drospirenone 3 mg and ethinyl estradiol 30 μg in the treatment of vasomotor symptoms. It was not prospectively designed to assess serum potassium.

Study 2
The amendment dated November 6, 2000 contains safety results from a single study. According to the medical reviewer, the information from this study does not provide additional relevant information beyond what he has previously reviewed. Therefore, a statistical assessment of the study results was not done.

This study, Study 97036[2], was designed to evaluate the efficacy and safety of drospirenone 3 mg and ethinyl estradiol 30 μg in the treatment of premenstrual syndrome and premenstrual dysphoric disorder. Serum potassium was measured at baseline and at 6 months; serum potassium levels are not mentioned in the inclusion or exclusion criteria for this study. Serum potassium was not a focus of the study.

Conclusion:
The HRT study and the oral contraceptive study were not designed prospectively to evaluate serum potassium levels. The studies may be underpowered to detect important outcomes. Moreover, levels were measured at baseline, 6 months and, for the HRT study, at 12 months. More frequent measurements of serum potassium, especially close to the time of starting study medication, are desirable. Therefore, these data are not sufficient to conclude no effect of drospirenone 3 mg and ethinyl estradiol 30μg on serum potassium levels.

Lisa A. Kammerman, Ph.D.
Team Leader, DB II

concur: E. Nevius, Ph.D. (HFD-715)

cc:
Archival NDA# 21-098
HFD-580/SMonroe, JBest, DHixon
HFD-715/ENevius, LKammerman
HFD-870/VJarugala, AParekh

[2] Title of Study 97036: A multicenter, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy of a monophasic oral contraceptive preparation, containing drospirenone 3 mg and ethinyl estradiol 30 μg, in the treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)

/s/

Lisa A. Kammerman
4/13/01 02:20:56 PM
BIOMETRICS

S. Edward Nevius
4/13/01 04:36:59 PM
BIOMETRICS
Concur with review.

APPEARS THIS WAY
ON ORIGINAL

JUN 23 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Biometrics Team Leader (HFD-715)

TO: Jeanine Best (HFD-580)

SUBJECT: NDA 21-098, Yasmin: labeling submitted June 22, 2000

I reviewed the section of Yasmin's labeling called "Interactions with drugs that have the potential to increase serum potassium," submitted by the applicant on June 22, 2000. I agree with the wording that describes the results of Study 98106.

/S/

Lisa A. Kammerman, Ph.D. 6/23/00

cc:
Archival NDA 21-098
HFD-580
HFD-580/JBest
HFD-715/Division files/Kammerman

APPEARS THIS WAY
ON ORIGINAL

Statistical Review and Evaluation
Clinical Studies[1]

NDA: 21-098

Applicant: Berlex

Name of drug: Yasmin 21/28 Tablets (drospirenone 3 mg and ethinyl estradiol 0.030 mg tablets)

Indication: Prevention of pregnancy

Documents reviewed: Amendment dated April 20, 2000; Amendment dated May 8, 2000; Amendment dated May 9, 2000; Amendment dated June 14, 2000

Medical reviewer: Scott Monroe, M.D. (HFD-580)

This statistical review evaluates evidence for the applicant's labeling claim of "no clinically or statistically significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo," so HFD-580 can decide final labeling.

HFD-580 asked this reviewer to (1) evaluate results of a repeated measures analysis of variance, and (2) comment on the results of a bioequivalence analysis.

My review concludes the data submitted do not support the applicant's claim of no statistically significant differences between the two treatment groups for serum potassium. A description of the study, results of the study, and my statistical review follow.

Description of study:
Study 98106[2] was designed as a bioequivalence study to compare twenty-four hour potassium serum summary measures between DRS/E2 and Placebo. Study 98106 was conducted at one study center. Twenty-four postmenopausal women were randomly assigned to either DRSP (3 mg)/E_2 (1 mg) oral tablet for 14 days, or a placebo oral tablet. All women took a background therapy of enalapril 10-mg oral tablet BID.

The primary serum potassium endpoints were $AUC_{(0\text{-}24\ hours)}$ and C_{max}. These were measured over a 24-hour period on Pretreatment Day 1 before administration of any study drug, and again on Treatment Day 14 after administration of DRSP/E2 or placebo. Thus, four primary endpoints were determined. Additionally, single potassium serum

[1] Keywords: Bioequivalence, active-control, non-inferiority
[2] Title of Study 98106: A double-blind, randomized, 2-parallel groups study to evaluate the potential for developing hyperkalemia when the hormone replacement therapy combination drug product drospirenone/estradiol is coadministered with an ACE inhibitor in postmenopausal women.

levels were measured on 2 occasions before treatment onset (at screening and on Pretreatment Day 2) and on Treatment Days 2, 4, 6, 8, 10, 12, and 15.

The four primary endpoints were log-transformed and then analyzed with analysis of covariance (ANCOVA) using baseline values (Pretreatment Day 1) as covariates.

A mean ratio comparing DRSP/E_2 and Placebo, $\mu_{DSRP/E2}/\mu_{Placebo}$, was estimated from the ANCOVA results for each primary endpoint:

a) AUC(0-24 hours), Pretreatment Day 1
b) Cmax, Pretreatment Day 1
c) AUC(0-24 hours), Day 14
d) Cmax, Day 14

Then, a 90% confidence interval was constructed for each mean ratio. Bioequivalence was concluded if the 90% two-sided confidence interval lay completely within the equivalence interval of 80% and 125%. These criteria are CDER policy for bioequivalence studies.

Results of the study:
The results show the 90% confidence intervals for the mean ratios of $AUC_{(0\text{-}24\ hours)}$, and of C_{max} fall within the bioequivalence interval of 80% and 125%. (See Table 6 of the amendment dated April 20, 2000 for the results.)

Therefore, the applicant concludes

- DRSP and Placebo are bioequivalent for serum potassium, and
- No statistically significant differences between DRSP and Placebo are observed for serum potassium.

Statistical review:
For the following reasons, the data do not support the applicant's labeling claim of no statistically significant differences between DRSP and Placebo.

1. According to the medical reviewer, observed serum potassium levels are the clinically relevant endpoints, not AUC nor Cmax. See his review for further discussion.

2. Because the clinically relevant endpoints are observed serum potassium levels, comparisons between treatment groups require a methodology different from the bioequivalence methodologies used in this study.

   The medical reviewer considers the change in serum potassium levels from pretreatment over time to be clinically relevant. Thus, he requested the applicant to submit a repeated measures analysis of variance, adjusted for serum potassium level on Pretreatment Day 2. The endpoints of the repeated measures analysis of variance are single serum potassium levels determined on Treatment Days 2, 4, 6, 8, 10, and 12.

A repeated measures analysis of variance adjusted for baseline, gives a p-value = .0661; see Amendment dated June 14, 2000. Therefore, the change in serum potassium levels over time among DRSP-treated subjects may differ from the change over time among Placebo-treated subjects.

The lack of statistical significance in this analysis does not mean "no difference." This study enrolled only 24 subjects; a larger study may have shown a statistically significant difference, because the power of the study would have been greater.

3. From a statistical perspective, the results from this study cannot be generalized to the population intended for use because
   - the study was conducted at a single center,
   - only 24 subjects were enrolled,
   - most of the subjects were Hispanic, and
   - all were postmenopausal.

4. For the results of the applicant's bioequivalence analyses to have been interpretable, the following would be needed:
   a) The endpoints[3] in the bioequivalence analyses are clinically relevant for assessing hyperkalemia.
   b) The ratio between DSRP and Placebo is the appropriate clinical metric for comparing the two treatment groups for hyperkalemia.
   c) The "equivalence" confidence interval limits are clinically relevant for hyperkalemia, rather than using the limits (80% to 125%) prescribed for bioequivalence analyses.
   d) Two-sided 95% confidence intervals are used.
   e) The two-sided 95% confidence intervals fall entirely within the clinically relevant "equivalence" intervals.

   As discussed above in Comment 1 and Comment 2, a) and b) do not hold for Study 98106. Further, Study 98106 does not address c) and d) and, therefore, e).

Recommendations:

1. Another study needs to be conducted to ensure a low occurrence rate of hyperkalemia. The study needs to be larger and may need to be more representative of the population intended for use.

2. The study objective and clinical endpoint need further clinical consideration. For example, a study objective may be the determination of the proportion of subjects who ever have a serum potassium level that exceeds the upper limit of normal. Then additional 24-hour serial measurements are needed to profile C_{max} over time.

[3] The average serum potassium level over 24 hours: $AUC_{(0\text{-}24\ hours)}$ at Day 14; the maximum serum potassium level over 24 hours: C_{max} at Day 14,

3. Study designs other than bioequivalence designs need to be considered. For example, a non-inferiority study is appropriate. A non-inferiority study requires two-sided 95% confidence intervals. The following *a priori* specifications are needed:
    - type of comparison, such as a difference or a ratio;
    - definition of clinically important values for the difference or ratio; and
    - a sample size with at least 80% power for a two-sided 95% confidence interval to rule out clinically important values.

Conclusion:
The results of this study suggest serum potassium changes over time for DRSP-treated subjects may differ from serum potassium changes over time for Placebo-treated subjects. Therefore, the evidence does not support the applicant's labeling claim of "no clinically or statistically significant differences observed in serum potassium concentrations in women given DRSP/E2 or placebo."

/S/

Lisa A. Kammerman, Ph.D. 6/20/00
Team Leader, DB II

concur: E. Nevius, Ph.D. (HFD-715) /S/

cc:
Archival NDA# 21-098
HFD-580/SMonroe, JBest, MMann
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APPEARS THIS WAY
ON ORIGINAL

MAR 0 2 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
STATISTICAL REVIEW AND EVALUATION

NDA:	21-098
Priority Classification:	1S
Applicant:	Berlex
Trade Name:	Yasmin® (Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg).
Indications:	Prevention of Pregnancy
Medical Officer:	Dena Hixon, M.D., HFD-580
Project Manager:	Jeanine Best, HFD-580

1.0 INTRODUCTION

1.1. Background

The applicant has submitted this NDA in support of Yasmin® (Drospirenone 3.0 mg and Ethinyl Estradiol 0.030 mg), an oral contraceptive for the prevention of pregnancy. They claim that this combination product possess both progestantinal and aldesterone-antagonist properties, similar to the profile of natural progestogen. They also claim that with this product, it might be possible to avoid side effects such as increases in blood pressure, retention of fluid, breast tenderness, and weight gain that are occasionally seen under conventional oral contraceptives.

The application included data from a total of 10 clinical studies conducted in the US and Europe. Only three studies included detail safety and efficacy data to support the following indication.

1.2. Indication

The indication for this product as proposed in the package insert is:

> *Yasmin® is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.*

1.3. Summary of Clinical Studies

To support the above indication, the sponsor has submitted safety and efficacy data from three Phase III studies, and seven other clinical studies conducted in Europe and the US. Table 1.3 shows the summary of safety and efficacy trials only. The NDA designated the first two

studies as "pivotal" and the third study as "supportive".

Table 1.3
Summary of Phase III Safety and Efficacy Studies

Study# / Location	Objectives	Study Design	Study Medication	Number of subjects*	Completed Cycles
92052/Europe	Safety/Efficacy	Open-label, Randomized, Multi-center, Parallel.	Yasmin® Marvelon®	442 445	26
96049/US	Safety/Efficacy	Open-label, Multi-center, uncontrolled.	Yasmin®	326	13
93044/Europe	Safety/Efficacy	Open-label, Randomized, Multi-center, Parallel	Yasmin® Marvelon®	1657 412	13

* Number of subjects who received study drugs.

This review will focus mostly on the efficacy results of the above Phase III studies. Detailed safety evaluation can be found in Medical Reviewer's report.

2.0 EVALUATION OF "PIVOTAL" STUDIES

2.1. European Study (#92052)

2.1.1. Study Description

The objective of this European study was to compare the contraceptive reliability, cycle control, duration and strength of bleeding and tolerance of Yasmin® (test drug) over Marvelon® (comparator). This was a multi-center, open-labeled, randomized, active control parallel group trial conducted at 26 centers in Europe. A total of 900 healthy menstruating women between ages of 18 and 35 years were randomized to receive either Yasmin® or Marvelon®. The study procedures included the following:

- A pregnancy test was performed prior to taking the first treatment tablet.
- The treatment phase began with the first day of menstrual cycle and ended on day 28 of the last treatment cycle (cycle 26).
- Both study drugs were taken for 21 days, followed by a 7-day tablet free interval in each cycle.
- Subjects were required to record days of tablet intake, days without bleeding, days with bleeding, forgotten or replaced tablet, and any adverse events on a menstrual chart provided by the investigator.
- Subjects were also required to record weekly weights on a weight chart.

The contraceptive efficacy assessment included:

- The occurrence of **intracyclic bleeding** (cycle control) during the 2nd until the 6th treatment cycle, the bleeding episodes recorded as none, scanty, normal/excessive.

- Contraceptive reliability using the pearl index (uncorrected and corrected) and pregnancy ratio. The pearl index and pregnancy ratio were defined as:

  Pearl index = 1300 x number of pregnancies divided by the number of cycles; and

  Pregnancy ratio = number of pregnancies occurring during the study period divided by the number of women taking at least 19 tablets in each cycle of the study period.

The study null hypothesis was that the two treatments do not differ (Ho: $Rate_Y = Rate_M$ versus $H_A : Rate_Y \neq Rate_M$) with respect to the rates of intracyclic bleeding at least once during cycles 2 to 6 of treatment against an alternative that the two treatments differ by a rate of 10%.

To detect such a difference (assuming 30% for Marvelon and 20% for Yasmin), the protocol needed 412 valid subjects per group, with a power of 90% at an error rate of 5%.

The intracyclic bleeding rate between the treatments was compared using $\chi 2$ test. No interim or subgroup analysis was planned in the protocol.

A valid case analysis (VCA) and an intent-to-treat (ITT) analysis population was used for the efficacy variables; however, the protocol did not explicitly define ITT subjects.

2.1.2. Results

Enrollment and Disposition: A total of 940 subjects were screened for inclusion in this study and 900 were randomized to receive the study drugs. Of these, 887 subjects received study drugs but thirteen subjects dropped out or were lost before study drugs were given. A total of 887 were available for intent-to-treat analysis and 718 were available for valid case analysis. The major reasons for not including 169 subjects in valid case analysis was due to missing data on intracyclic bleeding during cycles 2 to 6.

Demographic and Baseline features: The treatment groups were well balanced with respect to age, weight, body mass index, and ethnicity. Both treatment groups were also similar with respect to history of previous pregnancies, medical and surgery histories, menstrual history, and contraceptive use.

Primary Efficacy: The primary efficacy endpoint was the difference in the occurrence of at least one intracyclic bleeding during the treatment cycles 2 to 6 between the study drugs. Results of the sponsor's analysis (over 26 cycles) using both the ITT and VCA populations are shown in Table 2.1

As per protocol, the sponsor's null hypothesis that the treatment groups do not differ with respect to bleeding was not rejected. The occurrence of intracyclic bleeding for Yasmin group was comparable to Marvelon group although the rate of bleeding in Yasmin group was higher (30%) by 6 cycles of treatment than the rate (20%) assumed at the planning stage of this study. Both ITT and VCA analysis demonstrates that the study drugs were similar.

Table 2.1

Number and Percent of Women with at least one Intracyclic Bleeding

Analysis Population	Cycles	Yasmin*		Marvelon*		P-value
		n/N	%	n/N	%	(χ2 test)
Valid Case (n=718)	2-6	106/365	29.0	97/352	27.5	0.66
	2-13	127/333	38.1	123/326	37.7	0.91
	2-18	134/311	43.1	129/299	43.1	0.99
	2-26	130/279	46.6	145/281	51.6	0.24
ITT (n=887)	2-6	125/406	29.0	97/400	27.6	0.53
	2-13	146/370	39.4	140/365	38.4	0.76
	2-18	151/346	43.6	149/337	44.2	0.88
	2-26	148/311	47.6	167/314	53.2	0.16

n/N :Women with at least one bleeding / Total women in the cycle

Secondary Efficacy: The secondary efficacy variable was the contraceptive reliability based on number of pregnancies during the treatment cycles. A total of 6 women became pregnant during the treatment, three under Yasmin and three under Marvelon. Two measures of contraceptive reliability were calculated: Pearl index and pregnancy ratio. Table 2.2 shows the result of the sponsor's computation of both measures (uncorrected and corrected for other contraceptive use during the treatment cycles).

Table 2.2

Contraceptive Reliability as Measured by Uncorrected and Corrected Pearl Index and Pregnancy Ratio, European Study

	Treatment	All Cycles		Cycles 1-6		Cycles 1-13		Cycles 1-26	
		n/N	Index	n/N	Ratio	n/N	Ratio	n/N	Ratio
Pearl Index *	**Yasmin®**	3/9563	0.41						
	Marvelon®	3/9498	0.41						
Pregnancy ratio**	**Yasmin®**			1/390	0.26	1/343	0.29	3/278	1.08
	Marvelon®			1/387	0.26	1/336	0.30	3/274	1.09

* Pearl Index = # of Pregnancy x 13 x 100/Total complete cycles (N), ** Pregnancy Ratio = Pregnancies / # of cycle completers (N)

2.1.3. Reviewer's Comments

The sponsor's ITT population included 887 subjects and VCA population included 718 subjects, respectively (Table TT6, page 45, vol.183, Statistics) but in the primary efficacy analysis, 806 ITT subjects were used. Eighty-one (81) ITT subjects were not accounted for.

Our analysis confirms the sponsor's finding that Yasmin was an effective oral contraceptive. The present study demonstrates that the cycle control (assessed by intracyclic bleeding) was not statistically different between the test drug (Yasmin) and the comparator (Marvelon). Although intracyclic bleeding gradually increased over long term use (cycles 2 -26 compared to cycles 2 -6), the increase was not statistically different between the drugs. The contraceptive reliability (Pearl Index and Pregnancy Ratio) was also within acceptable (< 1.2, both uncorrected and corrected for other OC use) range; both measures were not statistically different between the treatment groups.

2.2. U.S. Study (#96049)

2.2.1. Study Description

The objective of this study was to evaluate the contraceptive efficacy and safety of Yasmin® tablets. This was an open-label, multi-center study conducted at 6 study centers in the US. A total of 333 healthy women of reproductive age, 18 to 35 years old, within 25% of ideal body weight, previous and current OC users, were enrolled in this study. All subjects were required

to have a negative pregnancy test within two weeks prior to the first dose of study drug. The study procedures included the following:

- All clinical, laboratory evaluations, and pregnancy test were performed at baseline.
- The treatment phase began with the first day of the menstrual cycle and ended on day 28 of each treatment cycle (cycle 1 to cycle 13).
- Subjects were required to fill out diary cards supplied by the sponsor to record the days that tablets were taken or omitted, menses and intermenstrual bleeding. All subject diaries were retrieved and evaluated at each visit (end of cycle 1, 3, 6, 9, and 13).
- Vital signs and adverse events were also monitored at the end of each visit.
- A second pregnancy test was performed at cycle 13 or at 3 months follow-up visit.

The contraceptive efficacy assessment included the computation of the Pearl Index, pregnancy ratio, and cycle control. The Pearl Index (number of pregnancies per 100 women-years) was computed based on (i) all cycles with use of other OCs, and (ii) cycles without use of other OCs. The pregnancy ratio was defined as the percent of women completing the study without any additional contraception and who become pregnant during the study. The cycle control was assessed by cycle length, length of menses and the number of days with breakthrough bleeding or spotting.

No hypothesis was formulated under this protocol and the patient enrollment was subjective. The statistical methods included only summary statistics and 95% confidence intervals to quantify the efficacy outcomes. No ITT analysis was planned.

Missing data were not replaced by any estimated or imputed values.

2.2.2. Results

Subject Enrollment and Disposition: A total of 333 subjects were enrolled at six study centers in this US study. Of these 333 subjects, 7 subjects discontinued before taking any study drugs. Another 106 subjects discontinued the study prematurely without completing the 13 required cycles as per protocol. The major reasons for discontinuation was listed as 'other' (12%) followed by withdrawal of consent (8%) and adverse event (6%). Therefore, a total of 220 subjects who completed all 13 cycles of treatment were used for efficacy analysis.

Demographic and Baseline features: Majority of the subjects (87%) enrolled were caucasians. The mean age of all the 326 subjects was 26.4 years with a mean body weight of 63 kg. A total of 176 (54%) were using oral contraceptives prior to enrolling in this study. They were

referred to as 'switchers' in this study. The remaining 150 subjects did not use OC in the cycle prior to this study but used other methods such as condom, diaphragm etc.

Primary Efficacy: The primary efficacy variable used was the Pearl Index and pregnancy ratio that required a calculation of the total number of cycles completed in the study. A subject was counted in the cycle if the subject completed the study drug for at least 19 of the cycles first 21 days.

One subject became pregnant during the study. The Pearl Index and pregnancy ratio, both uncorrected and corrected, are shown in Table 2.3. The corrected Pearl Index of 0.40 and pregnancy ratio of 0.45 is much lower in this study than the acceptable threshold of 1.4.

Table 2.3
Pearl Index and Pregnancy ratio, US Study

Number of Pregnancies	1
Total number subjects who completed 13 cycles	220
Total cycles completed	3201
Total cycles completed without other contraception	3192
Uncorrected Pearl Index	0.40
Corrected Pearl Index	0.40
Uncorrected Pregnancy Ratio	0.45
Corrected Pregnancy Ratio	0.45

Secondary Efficacy: The secondary efficacy variable cycle control that included cycle length, duration of withdrawal bleeding, and intermenstrual bleeding. The median cycle length for all subjects in cycle 2 through 13 was 28 days and the median duration of withdrawal bleeding was 5 days in cycles 1 through 13. A total of 151 (51%) subjects reported intermenstrual bleeding in at least 1 cycle during the study.

2.2.3. Reviewer's Comments

A significant number of subjects (32%) discontinued the study prematurely and approximately 50% used other contraceptives prior to enrolling in this study. It was not clear from the study report if the subjects had a reasonable wash out period. Only one pregnancy occurred during the study and the contraceptive effectiveness of Yasmin was shown by the Pearl index of 0.40, lower than acceptable threshold of 1.4. The sponsor's analysis demonstrates that Yasmin is an effective oral contraceptive but the effectiveness could have been biased by the concomitant effect of other OC use.

2.3. European Study (#93044)

2.3.1. Study Description

The objectives of this European study were to compare contraceptive reliability, cycle control and the tolerance of Yasmin and the active comparator, Marvelon. This open-label randomized study was conducted in 8 European countries at 80 study centers. Healthy menstruating women ages 18 to 35 years old seeking oral contraception and meeting other inclusion criteria, were randomized to receive either Yasmin or Marvelon at 4:1 ratio. Assuming a 10% difference in bleeding rate (cycle control) between the test and the comparator, the study was sized to enroll 2085 subjects, adjusting for a 40% drop out rate.

Both study drugs were taken orally for 21 consecutive days, followed by a 7-day tablet free interval for a total of 13 cycles. All subjects were required to record tablet intake and bleeding days in each cycle on the menstrual charts provided by the investigator.

The primary efficacy variable was the cycle control, measured by the occurrence of intracyclic bleeding during the 2nd until the 13th treatment cycle. The secondary efficacy variable was the contraceptive reliability measured by Pearl Index and Pregnancy Ratio.

The study null hypothesis was that the two treatments do not differ with respect to the rates of intracyclic bleeding one time during cycles 2 to 13 of treatment. The bleeding rates between the treatment groups were compared using the $\chi 2$ test.

A valid case analysis (VCA) and an intent-to-treat (ITT) analysis population were used for the efficacy variables. A subject was considered as a valid case if her treatment cycles 1 to 13 were all valid. The ITT population was not defined clearly.

2.3.2. Results

A total of 2098 subjects were randomized, 1680 to Yasmin and 418 to Marvelon. Of these 2098 subjects, 2069 subjects were available for ITT and 1209 for VCA analysis. For both ITT and VCA analysis population, the treatment groups were comparable with respect to age, body mass index, ethnicity, gynecological and obstetric history. Approximately, 60% of the subjects in both treatment groups had used oral contraceptives in the last cycle before treatment.

The contraceptive effectiveness, as measured by the intracyclic bleeding rate, was calculated for treatment cycles 2 to 13 using both VCA and ITT analysis population. The sponsor's analysis demonstrated that two treatments did not differ with respect to bleeding rate (30% and 31%, $p>0.80$; for Yasmin and Marvelon, respectively) using VCA population ($N=1189$ for both treatment groups). Analysis using ITT population ($N=1626$ for both treatment groups)

yielded the same conclusion. Results during cycles 2 to 6 were also similar using both VCA and ITT population. In either case, the null hypothesis that the two treatments do not differ with respect to intracyclic bleeding could not be rejected.

The contraceptive reliability measured by the Pearl Index and pregnancy ratios, were calculated based on number of pregnancies during the treatment cycles. There were 11 pregnancies reported during study medication (10 in Yasmin and 1 in Marvelon group). The uncorrected Pearl Index were 0.70 and 0.28 for Yasmin and Marvelon, respectively. Correcting for other OC use, the index was similar. The pregnancy ratios were 0.80 and 0.31 for Yasmin and Marvelon during cycle 1 to 13. Both measures showed that the contraceptive reliability of Yasmin was significantly lower than Marvelon.

2.3.3 Reviewer's Comments

As per protocol, all patients who received the study drugs should be in the ITT analysis, yet the sponsor's analysis population included a total of 1626 subjects instead of 2069 subjects as specified in Table TT7 (study report) for the primary target variable (intracyclic bleeding). Besides, the definition of ITT population was not clear.

In this large European study although the cycle control between the study drugs was statistically similar, the contraceptive reliability for Yasmin was inferior to Marvelon.

As per safety, the Yasmin group had statistically significant weight reduction compared to Marvelon group.

3.0 Reviewer's Conclusion

The sponsor has submitted safety and efficacy data from three Phase III studies to demonstrate the effectiveness of Yasmin as an oral contraceptive. Of the two "pivotal" studies, the European study was a randomized, parallel group, active control study while the U.S. study was an open-label study. The "supportive" European study was also a randomized, active control study conducted in 8 different countries. Although the NDA identified two of the studies as "pivotal" (92052, 96049) and one as "supportive" (93044), the NDA does not address the reasons for these classifications. Presumably, because the third study showed Yasmin to be inferior to Marvelon, the sponsor considered this one as "supportive".

The first European study (#92052) was primarily designed to demonstrate the contraceptive effectiveness of Yasmin compared to Marvelon. Contraceptive effectiveness was assessed by the cycle control and contraceptive reliability. The sponsor's analysis, as well as our analysis, indicates that the cycle control was not different for Yasmin compared to Marvelon during the treatment period. There were 3 pregnancies during the 26 cycles of treatment and the Pearl Index and pregnancy ratios were within acceptable range and similar between both the study drugs. Though this study demonstrates contraceptive effectiveness, problems with the conduct of the study particularly with regard to missing data and lack of wash out period could have biased the results. However, only 3 pregnancies were reported and the Pearl Index was 0.40, which was below the range. Therefore, the evidence shown in this European study support the sponsor's proposed claim that Yasmin prevents pregnancy.

The US study (study #96049) was also designed to demonstrate the contraceptive effectiveness of Yasmin, but unlike the European study, no control was used in this study. Almost a third (32%) of the study subjects discontinued the study prematurely. Approximately 50% of the remaining subjects used other contraceptives prior to switching to Yasmin. The study protocol did not plan wash out period for the switchers. During 13 cycles of treatment, one pregnancy occurred and the Pearl index was 0.40, similar to the index shown in the European study. Although the study was an open-label, and non-comparator study, the results were consistent with the European active control study.

The "supportive" European study (#93044) was designed to demonstrate the efficacy and safety of Yasmin compared to Marvelon in a much larger number of study subjects (N=2069). Subjects were randomized to receive either Yasmin or Marvelon in a 4:1 ratio. Approximately, 60% of the subjects were using other oral contraceptives in the last cycle before the current study drugs were given. There was lack of clarity on the ITT population used in the anlysis. During 13 cycles of treatment, 11 pregnancies were reported (10 in Yasmin and 1 in Marvelon) yielding a Pearl Index of 0.70 and 0.28 for Yasmin and Marvelon, respectively. The cycle control was similar between the treatments. But unlike the other European phase III study, which also used Marvelon as a control, the contraceptive reliability of Yasmin was statistically significantly worse than Marvelon.

Overall, the Pearl Index estimates from the three Phase III studies demonstrate that Yasmin was effective in cycle control. In addition, for one of the two studies that used Marvelon as a comparator, Yasmin was statistically significantly worse than Marvelon in preventing pregnancy, while the two treatments appeared "similar" in the other study.

/S/

Mahboob Sobhan, Ph.D.
Reviewing Statistician, HFD-715

/S/

Concur:

Lisa Kammerman, Ph.D.
Team Leader, HFD-715

cc:
Archival NDA 21-098
HFD-580/Best, Hixon
HFD-715/Kammerman, Sobhan, Nevius

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

To: NDA 21-098 action package

From: Venkat Jarugula, Ph.D.
Reviewer, HFD-870

Through: Ameeta Parekh, Ph.D.
Team Leader, HFD-870

Re: NDA 21-098 Labeling

Date: May 10, 2001

The human pharmacokinetics and Bioavailability (Section 6) of NDA 21-098 for Yasmin has been found acceptable by the review of original NDA (refer to Biopharm review dated 2/24/00). No new information is submitted to Section 6 of NDA 21098 for review. The following minor changes are recommended to the sponsor's draft physician's label dated 11/06/00.

On page 3, under Food Effect section, the first sentence should be changed as " The rate of absorption of DRSP and EE following single administration of two YASMIN 28 tablets was slower.....".

On page 3, under distribution section, second and third sentences should be combined to read as " The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4 – 5 L/kg."

The above recommended changes have been incorporated by the sponsor in the proposed labeling dated 5/9/01. Therefore, the sponsor's proposed physician label dated 5/9/01 is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Venkateswar Jarugula
5/10/01 01:01:06 PM
BIOPHARMACEUTICS

Ameeta Parekh
5/11/01 03:14:12 PM
BIOPHARMACEUTICS
I concur

JUN 22 2000

MEMORANDUM

Date: 06-21-2000

From: Venkateswar R. Jarugula, Ph.D. /S/ 6/22/00
Reviewer, HFD-870

Through: Ameeta Parekh, Ph.D. /S/ 6/22/00
Team Leader, HFD-870

To: NDA 21-098 (Yasmin)

Subject: Addendum to Clinical Pharmacology and Biopharmaceutics review of Yasmin dated 06/15/00

The objective of this memo is to correct the error in numbers listed in the table of pharmacokinetic parameters (from renal impairment study) reported in the Clinical Pharmacology and Biopharmaceutics review of Yasmin dated 06/15/00. The geometric mean pharmacokinetic parameters, $AUC_{0\text{-tlast}}$ (N=7) and $AUC_{0\text{-}\infty}$ (N=6) for moderate renal impairment group in the above mentioned table should be 2261 (58% CV) and 2059 (35% CV) ng.h/ml, respectively. The $AUC_{0\text{-}\infty}$ for subject No.26 in the moderate impairment group was not calculated by the sponsor because of lack of sufficient number of data points for calculating terminal elimination half-life for this subject. As a result the mean $AUC_{0\text{-}\infty}$ and $t_{1/2}$ were calculated from only 6 subjects' data in the moderate impairment group. The information reported in the labeling of Yasmin is not affected by this memo.