CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-544

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

NDA:	21-544
Name of Drug:	Seasonale (levonorgestrel (150 µg); ethinyl estradiol (30 µg))
Indication:	Oral contraceptive for the prevention of pregnancy
Sponsor:	Barr Research, Inc.
Documents Reviewed:	Study Reports and the data submitted to Electronic Document Room:
	Paper Volumes (August 5, 2002) 1.1-1.2, 1.76-1.95
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Date Received:	August 7, 2002
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Key Words:	Clinical studies, NDA review, One Study Application.

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The effectiveness of Seasonale extended therapy regimen in the prevention of pregnancy has been demonstrated but the increased risk of unanticipated spotting or bleeding for Seasonale users needs to be taken into consideration in the overall decision about the efficacy benefit of Seasonale.

This result is based on a single, multi-center, open label, randomized, parallel-group study comparing the safety and efficacy to prevent pregnancy of the oral contraceptives Seasonale, the test product, and Nordette, the comparator, in sexually active women aged 18 to 35 years of childbearing potential over one year of use. The reason for developing Seasonale is to decrease the frequency of menses and menses-related complaints. Seasonale is an extended regimen oral contraceptive therapy (four 91-day cycles per year) and Nordette is a conventional regimen oral contraceptive therapy (13 28-day cycles per year). Both products are composed of 150 µg levonorgestrel and 30 µg ethinyl estradiol.

Efficacy is based on calculation of pregnancy rates using the Pearl Index in women aged 18 to 35 years. The Pearl Index is 1.98 for Seasonale (95% C.I. from 0.02% to 2.50%) and 2.22 for Nordette (95% C.I. from 0% to 3.98%). In addition to efficacy, study discontinuation rates for adverse events should be considered. Discontinuation due to adverse events is different between the Seasonale and Nordette groups, especially when adverse events are characterized as "unacceptable bleeding" (unanticipated spotting or bleeding, that is, spotting or bleeding at times other than the 7 days of withdrawal from active product for menses to occur) or other. Seasonale has a greater percentage of subjects (6.1%) discontinuing due to "unacceptable bleeding" than Nordette subjects (1.5%) in women aged 18 to 35 years.

Given that the rationale for developing Seasonale is to decrease the frequency of menses and menses-related complaints, the increased percentage of unanticipated spotting or bleeding for Seasonale needs to be taken into account by the clinical reviewer in the overall labeling and regulatory decision for Seasonale.

2 BACKGROUND AND INDICATION

Study SEA301 was designed to demonstrate the efficacy and safety of two dosage levels of Seasonale extended regimen (91-day) oral contraceptive therapy over the course of one year in sexually active women, 18-35 years of age, who desired pregnancy prevention. The reason for developing Seasonale was to decrease the frequency of menses and menses-related complaints. Table 2.1 presents a brief summary of study SEA301.

Table 2.1
Brief Summary of Study SEA301

Study Number (Dates Conducted)	Number of Centers (Location)	Treatment	Sample Size (ITT*)	Duration of Treatment	Design
SEA301 (7-12-00 to 3-7-02)	47 (USA)	Seasonale Nordette Seasonale Ultra-Lo Levlite	456 226 463 231	Four 91-day cycles Thirteen 28-day cycles Four 91-day cycles Thirteen 28-day cycles	Open Label, Randomized, Parallel Group

Source: Statistical reviewer's listing.
* The ratio of Seasonale and Seasonale Ultra-Lo subjects to Nordette and Levlite subjects was planned to be 2:1.

The Division of Reproductive and Urologic Drug Products agreed to accept a single study because Seasonale is bioequivalent to Nordette (both are composed of 150 µg levonorgestrel and 30 µg ethinyl estradiol) and the sponsor owns an approved generic form of Nordette (which is the pill used in this study). The difference is in the regimen for the product, a 91-day treatment regimen for Seasonale (84 days of active product + 7 days of inactive product) versus a 28-day treatment regimen for Nordette (21 days of active product + 7 days of inactive product).

During the review, I could not replicate the primary efficacy analysis results originally submitted by the sponsor. The Division requested that the sponsor address the discrepancy and to check all other supportive analyses of the primary efficacy variable. The sponsor concurred with my analysis results and submitted corrected primary

efficacy and other affected supportive analyses of the primary efficacy variable in the May 1, 2003 and May 5, 2003 (letter date) submissions. The discrepancy was due to an error in the sponsor's SAS computer code. The sponsor results presented in this review are from these revised analyses.

The sponsor's proposed indication is:

Seasonale oral contraceptive tablets are indicated for the prevention of pregnancy.

Since the sponsor is seeking approval for Seasonale and not for Seasonale Ultra-Lo, this review will focus on the results for Seasonale and Nordette for the primary efficacy group of 18 to 35 year old women.

3 STUDY DESIGN

3.1 Study Description

Study SEA301 is a multi-center (47 U.S. centers), open label, randomized, parallel-group study comparing Seasonale and Seasonale Ultra-Lo with Nordette and Levlite (active controls), respectively. Sexually active women aged 18 to 40 years of childbearing potential who satisfied the inclusion criteria, which included a negative urine pregnancy test and agreement to use the study oral contraceptive therapy as their primary birth control method, were randomly assigned to one of the four treatment groups. The study was divided into four 91-day cycles for Seasonale/Seasonale Ultra-Lo and 13 28-day cycles for the Nordette/Levlite subjects. Subjects were instructed to take one tablet daily and evaluations for efficacy and safety were scheduled at seven specified office visits. Subjects entered data into an electronic diary that had an audible daily reminder and allowed data entry only for the day of use or into a back-up paper diary on a daily basis. Subjects were to be followed for two months following completion of the study or early withdrawal for the occurrence of pregnancy.

3.2 Primary Objective and Efficacy Variable

The primary objectives of this study are to demonstrate the efficacy and safety of Seasonale 91-day oral contraceptive therapy compared to Nordette 28-day oral contraceptive therapy. The Pearl Index for the group of treated subjects 18-35 years of age is the primary efficacy variable.

3.3 Statistical and analytical plans

The primary efficacy analysis consists of the calculation of the Pearl Index using all on treatment pregnancies, completed cycles, and excluding any cycles where other birth control methods was used in the group of treated subjects 18-35 years of age. The Pearl Index for each group is defined as follows:

Nordette Pearl Index = 100 × (number of pregnancies) × (13 cycles/year) / (total number of 28-day cycles completed)

Seasonale Pearl Index = 100 × (number of pregnancies) × (4 cycles/year) / (total number of 91-day cycles completed)

Pregnancy life table analysis in the same group of subjects is also performed as supportive evidence. Cumulative pregnancy rates at 52 weeks are estimated using the life table method and 28-day intervals for Nordette and 91-day intervals for Seasonale using all completed cycles.

No formal statistical comparisons and no formal Pearl Index threshold to meet were planned. All subjects' data for total exposure up to the time of loss, pregnancy, or completion of study was used in the efficacy analysis.

4 STUDY RESULTS

4.1 Subject Enrollment, Randomization, Disposition, and Demographics

Table 4.1 presents the number of randomized subjects and the disposition of treated subjects 18-35 years of age. A greater percentage of Seasonale subjects (43.6%) discontinued study than Nordette subjects (29.2%). The primary reason for study discontinuation is adverse events, with a greater percentage of Seasonale subjects (15.4%) than Nordette subjects (9.7%) discontinuing. The adverse events can be further characterized as being

due to "unacceptable bleeding" (unanticipated spotting or bleeding, that is, spotting or bleeding at times other than the 7 days of withdrawal from active product for menses to occur) or other. With this characterization, Seasonale has a greater percentage of subjects (6.1%) discontinuing due to "unacceptable bleeding" than Nordette subjects (1.5%). A more detailed discussion of unanticipated bleeding is found in the clinical review. A greater percentage of subjects in the Seasonale group (11.1%) than the Nordette group (2.6%) discontinued due to subject decision. Most of the Seasonale subjects discontinued due to social reasons, for example, moved away from the area.

Table 4.1
SEA301: Randomized Subjects and Disposition of All Treated Subjects 18-35 Years of Age

	Seasonale	Nordette
Randomized	464	230
Treated (ITT)	456	226
Treated, 18-35 Years of Age n (%*)	397 (85.6)	195 (84.8)
Discontinued n (%**)	173 (43.6)	57 (29.2)
Primary Reason for Discontinuation n (%):		
Adverse Event	61 (15.4)	19 (9.7)
Adverse Event Other than "Unacceptable Bleeding"	*37 (9.3)*	*16 (8.2)*
"Unacceptable Bleeding" as an Adverse Event	*24 (6.1)*	*3 (1.5)*
Subject Decision	44 (11.1)	5 (2.6)
Non-compliant	22 (5.5)	9 (4.6)
Lost to Follow-up	37 (9.3)	19 (9.7)
Pregnant	4 (1.0)	3 (1.5)
Investigator Discretion	2 (0.5)	1 (0.5)
Other/Unknown	3 (0.8)	1 (0.5)

Source. Table 3.1, Vol. 1.76, page 10-000138 and Table 3.2.2, Vol. 1.76, page 10-000141.
* With respect to number of treated subjects.
** With respect to number of treated subjects 18-35 years of age.

Of the treated subjects aged 18-35 years, the mean age is 26 years and the majority (>75%) of subjects are Caucasian. The Seasonale and Nordette treatment groups are comparable in race and age.

4.2 Sponsor's Efficacy Results and Conclusion

Table 4.2 presents the Pearl Index for all treated subjects 18-35 years of age. Seven total pregnancies occur in three Nordette and four Seasonale subjects. The Pearl Index is 1.97 for Seasonale and 2.22 for Nordette.

Table 4.2
SEA301: Pearl Index Calculation of Treatment Failure Rates:
Completed Cycles Only – All Treated Subjects 18-35 Years of Age
Excluding Cycles Where Any Use of Other Birth Control Method Was Reported

Treatment	Number of On-Treatment Pregnancies	Number of Completed Cycles	Pearl Index
Nordette	3	1759	2.22
Seasonale	4	811	1.97

Source: Table 6.1.3.2, Vol. 1.76, page 10-000160 (revised by sponsor and submitted on May 1, 2003)

The life table estimates of pregnancy rates using all completed cycles are 1.24% for Nordette (28-day cycle; 95% C.I. from 0% to 2.94%) and 1.17% for Seasonale (91-day cycle; 95% C.I. from 0.02% to 2.32%) [from Table 6.2.1.1, Volume 1.76, page 10-000178].

Based on the above results, the sponsor concludes the efficacy of Seasonale extended regimen oral contraceptive (OC) therapy is comparable to that observed for conventional 28-day OC therapy at the same dose. The Pearl Index in treated subjects 18-35 years of age (complete cycles) was 1.97 for Seasonale vs. 2.22 for Nordette.

4.3 Reviewer's Efficacy Analyses

Table 4.3 presents the Pearl Index for all treated subjects 18-35 years of age. There are seven total pregnancies identified, three in Nordette subjects and four in Seasonale subjects. The Pearl Index is 1.98 for Seasonale and 2.22 for Nordette.

Table 4.3

SEA301: Pearl Index Calculation of Treatment Failure Rates: Completed Cycles Only – All Treated Subjects 18-35 Years of Age – Excluding Cycles Where Any Use of Other Birth Control Method (BCM) Was Reported

Treatment	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Pearl Index	95% Confidence Interval
Nordette	188	3	2054	296	2.22	(0.46, 6.38)
Seasonale	387	4	1074	265	1.98	(0.54, 5.03)

Source: Statistical reviewer's listing.

The life table estimates of pregnancy rates using all complete cycles are 1.87% for Nordette (28-day cycle; 95% C.I. from 0% to 3.98%) and 1.26% for Seasonale (91-day cycle; 95% C.I. from 0.02% to 2.50%).

4.4 Conclusions

From a statistical standpoint, the sponsor has provided one study that is well controlled and adequate for demonstrating the effectiveness of Seasonale extended therapy regimen in the prevention of pregnancy. Although Seasonale's efficacy may be comparable to that of Nordette, the increased risk of unanticipated spotting or bleeding for Seasonale users needs to be taken into consideration in the final decision about Seasonale's efficacy benefit.

5 APPENDIX

The following are tables of additional analyses requested by the Medical Reviewer and performed by the Statistical Reviewer. Analyses that exclude Site 1 are done because the investigator has a vested interest in the development of Seasonale and the Medical Reviewer is interested in knowing if Site 1 has an undue influence on the results of the study.

Table 5.1
SEA301: Pearl Index Calculation of Treatment Failure Rates: Completed Cycles Only
All Treated Subjects 18-35 Years of Age
Excluding Cycles Where Any Use of Other Birth Control Method (BCM) Was Reported and Excluding Site 1

Treatment	N	Number of Pregnancies	Number of Cycles	Number of BCM Cycles	Pearl Index	95% Confidence Interval
Nordette	174	3	1882	282	2.44	(0.51, 7.01)
Seasonale	368	4	1013	263	2.13	(0.59, 5.42)

Source: Statistical reviewer's listing.

Table 5.2
SEA301: Pearl Index Calculation of Treatment Failure Rates: Completed Cycles Only
All Treated Subjects 18-35 Years of Age -No Cycles Excluded

Treatment	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Nordette	188	3	2054	1.90	(0.39, 5.46)
Seasonale	387	4	1074	1.49	(0.40, 3.79)

Source: Statistical reviewer's listing.

The Pearl Indices in Table 5.2 agree with the sponsor's Pearl Indices of 1.90 for Nordette and 1.49 for Seasonale (sponsor revised Table 6.1.5.2, Vol. 1.76, page 10-000164).

Table 5.3
SEA301: Pearl Index Calculation of Treatment Failure Rates: Completed Cycles Only
All Treated Subjects 18-35 Years of Age -No Cycles Excluded and Excluding Site 1

Treatment	N	Number of Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Nordette	174	3	1882	2.07	(0.43, 5.96)
Seasonale	368	4	1013	1.58	(0.44, 4.01)

Source: Statistical reviewer's listing.

The following two Seasonale analyses use a "28-day" cycle that is calculated by taking the total number of days on treatment (SAS variable DATINTT) and dividing it by 28 to obtain the number of "28-day" Seasonale cycles where subjects are at risk for pregnancy.

Table 5.4
Seasonale "28-day" Cycle Analysis for Two Different Situations
Completed Cycles Only - All Treated Subjects 18-35 Years of Age –
Excluding Cycles Where Any Use of Other Birth Control Method (BCM) Was Reported

Situation	N	Number of Pregnancies	Number of Cycles	Number of BCM Cycles	Pearl Index	95% Confidence Interval
All sites	387	4	3640.32	997	1.97	(0.53, 5.01)
Without Site 1	368	4	3439.04	960	2.10	(0.58, 5.33)

Source: Statistical reviewer's listing.

The life table estimate of the pregnancy rate using all completed 28-day cycles for Seasonale is 1.29% (95% C.I. from 0.02% to 2.56%).

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/s/

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Concur with review.

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