CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-840

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW
Labeling

NDA/Serial Number:	21-840 / 000
Drug Name:	Seasonique (Levo 150 μg/EE 30 μg + EE 10 μg) oral contraceptive
Indication(s):	Prevention of pregnancy
Applicant:	Duramed
Date(s):	Letter Date: March 24, 2006 PDUFA Date: May 27, 2006
Biometrics Division:	Division of Biometrics 2, HFD-715
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Division Director:	Ed Nevius, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	Ronald Orleans, M.D., Medical Reviewer Shelley Slaughter, M.D., Team Leader
Project Manager:	Jennifer Mercier
Key Words:	Labeling review

The Sponsor has resubmitted this NDA for Seasonique Tablets as a complete class 1 response to the August 17, 2005 approvable (AE) action letter and the letter regarding their dispute with the Division of Reproductive and Urologic Drug Products from the Office of New Drugs. This is a labeling review and no further efficacy evaluation is needed. I have reviewed the Sponsor's proposed "Indications and Usage" section of the label and submit the following wording describing pivotal study PSE-301 and its results.

INDICATIONS AND USAGE

Seasonique™ tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

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/s/

Sonia Castillo
5/10/2006 12:25:49 PM
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S. Edward Nevius
5/11/2006 04:50:16 PM
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Concur with review.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Serial Number:	21-840 / 000
Drug Name:	Seasonique (Levo 150 μg/EE 30 μg + EE 10 μg) oral contraceptive
Indication(s):	Prevention of pregnancy
Applicant:	Duramed
Date(s):	Letter Date: October 21, 2004 PDUFA Date: August 19, 2005
Review Priority:	1S
Biometrics Division:	Division of Biometrics 2, HFD-715
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Michael Welch, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	Ronald Orleans, M.D., Medical Reviewer Shelley Slaughter, M.D., Team Leader
Project Manager:	Karen Kirchberg
Key Words:	Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Seasonique 10 µg 91-day extended regimen oral contraceptive has demonstrated a Pearl Index of 1.77 (95% confidence interval is 0.71 to 3.64), which is consistent with other approved oral contraceptive products.

1.2 Background

The Sponsor has submitted two, multi-center, open label, uncontrolled, randomized, parallel-group studies (one pivotal and one supportive) comparing the safety and efficacy of Seasonique oral contraceptive to prevent pregnancy, in sexually active women aged 18 to 35 years of childbearing potential over one year of use. Seasonique 10 µg is a 91-day extended regimen oral contraceptive composed of 150 µg levonorgestrel (LNG) and 30µg ethinyl estradiol (EE) for the first 84 days of a 91-day cycle and 10µg EE for the last 7 days of a 91-day cycle.

Seasonale (reference NDA 21-544) is composed of 150 µg levonorgestrel and 30 µg ethinyl estradiol. Seasonique's formulation is similar to Seasonale during the first 84 days of the 91-day treatment regimen: 150 µg LNG + 30 µg EE. The difference between Seasonique and Seasonale is the formulation during the last 7 days of the 91-day treatment regimen: 10 µg EE for Seasonique vs. inactive product for Seasonale.

The Sponsor's proposed indication is:

[redacted]

1.3 Statistical Issues and Findings

There is one statistical issue with this submission: the Medical Reviewer has identified two additional pregnancies in the pivotal study and they will be used to calculate the Pearl Index.

Efficacy is based on calculation of pregnancy rate using the Pearl Index in women aged 18 to 35 years. In the pivotal study, the Pearl Index for Seasonique 10 µg is 1.77 (95% C.I. from 0.71% to 3.64%).

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted two, multi-center, open label, uncontrolled, randomized, parallel-group studies designed to demonstrate the safety and efficacy of two dosage levels of the 91-day extended regimen oral contraceptive Seasonique in sexually active women aged 18 to 35 years who desire pregnancy prevention over one year of use. Study PSE-301 is the pivotal study and study PSE-302 is a smaller study designed to evaluate endometrial protection via description of the incidence of endometrial hyperplasia to support safety and provide supportive evidence of efficacy. Table 2.1 presents a brief summary of the two studies.

Table 2.1
Brief Summary of Clinical Studies for Seasonique

Study Number (No. of Centers / Country) and Dates of Study Conduct	Treatment[1]	Sample Size Randomized (Treated)	Duration of Treatment	Design[2]
PSE-301 (36 / U.S.) 4-14-02 to 4-8-04	DP3-84/30: LNG (150 µg) /EE (30 µg) x 84 days, followed by EE 30 µg x 7 days	DP3-84/30: 1025 (1013) DP3-84/10: 1024 (1006) **Total: 2049 (2019)**	Four 91-day cycles	OL, R, PG, MC, U
PSE-302 (7 / U.S.) 4-28-02 to 4-13-04	DP3-84/10: LNG (150 µg) / EE (30 µg) x 84 days, followed by EE 10 µg x 7 days	DP3-84/30: 96 (95) DP3-84/10: 95 (95) **Total: 191 (190)**		

Source: Statistical reviewer's listing.
[1] LNG = levonorgestrel, EE = ethinyl estradiol, both treatment groups are included in both studies PSE-301 and PSE-302
[2] OL = Open Label, R = Randomized, PG = Parallel Group, MC = Multicenter, U = Uncontrolled

The Sponsor's proposed indication is:

[redacted]

Since the Sponsor is seeking approval for Seasonique 10 µg and not for Seasonique 30 µg, this review will focus on the results for Seasonique 10 µg in the group of 18 to 35 year old women.

2.2 Data Sources

The study reports and additional information for these studies are submitted electronically and in paper format. The submitted SAS data sets for both studies are complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\N21840\N_000 under various submission dates ranging from 10-21-2004 to 12-01-2004. The one paper document is dated 12-14-2001.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Pivotal study PSE-301 is a multi-center, open label, uncontrolled, randomized, parallel-group study of Seasonique 10 µg 91-day oral contraceptive therapy. 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 two treatment groups. The study was divided into four 91-day cycles. Subjects were instructed to take one tablet daily and entered data into an electronic diary that allowed data entry only for the day of use on a daily basis. Subjects were to be followed for three months following completion of the study or early withdrawal for the occurrence of pregnancy.

The primary objectives of study PSE-301 are to demonstrate the efficacy and safety of Seasonique 10 µg 91-day oral contraceptive therapy. The Pearl Index for subjects 18-35 years of age is the primary efficacy variable. The Pearl Index is calculated using all on treatment pregnancies, completed cycles, and excluding any cycles where other birth control methods (BCM) was used and is defined as follows:

Pearl Index = 100 × (number of pregnancies) × (4 cycles/year) / (total # of 91-day cycles completed excluding cycles where other BCM was used)

No formal Pearl Index threshold to meet or statistical hypothesis tests were planned.

Although the design of study PSE-302 is similar to study PSE-301, it is a smaller study whose purpose is to evaluate endometrial protection and provide supportive evidence of efficacy. Its results are presented for completeness.

3.1.1 Overall Study Descriptive Statistics

Table 4.1 presents the number of randomized subjects and the disposition of treated subjects 18-35 years of age. The primary reason for study discontinuation in study PSE-310 is "subject decision" (12.4%) and in study PSE-302 is "lost to follow-up" (15.1%). Also, of the treated subjects aged 18-35 years, the mean age is 26.2 years in study PSE-301 and 25.9 years in study PSE-302; and the majority (>65%) of subjects are Caucasian in both studies.

Table 4.1
Studies PSE-301 and PSE-302: Randomization and Disposition of All Treated Subjects 18-35 Years of Age for Seasonique 10 µg

	PSE-301	PSE-302
Randomized	1024	95
Treated (ITT)	1006	95
Treated, 18-35 Years of Age n (%*)	708 (70.4)	73 (76.8)
Discontinued n (%**)	274 (38.7)	34 (46.6)
Primary Reason for Discontinuation n (%**):		
Adverse Event	71 (10.0)	7 (9.6)
Subject Decision	88 (12.4)	7 (9.6)
Non-compliant	21 (3.0)	4 (5.5)
Lost to Follow-up	83 (11.7)	11 (15.1)
Pregnant	3 (0.4)	1 (1.4)
Investigator Discretion	1 (0.1)	0 (0.0)
Other/Unknown	7 (1.0)	4 (5.5)

Source: Tables 2 and 3.3, pages 51 and 54, Study PSE-301 report; Tables 2 and 3.3, pages 58 and 60, Study PSE-302 report; and document DC4.PDF for Study PSE-301 and document DC4.PDF for Study PSE-302 from the December 1, 2004 submission.
* With respect to number of treated subjects.
** With respect to number of treated subjects 18-35 years of age.

3.1.2 Study PSE-301 Results

Table 4.2 presents the Pearl Index results for Seasonique 10 μg in supportive study PSE-301 in all treated subjects 18-35 years of age for the Sponsor and Reviewer. The Sponsor reports five pregnancies and a Pearl Index of 1.27. The Reviewer reports seven pregnancies and a Pearl Index of 1.77.

Table 4.2
Study PSE-301: Results for Sponsor and Reviewer - Pearl Index Calculation of Treatment Failure Rates for Seasonique 10 μg: Completed Cycles Only – All Treated Subjects 18-35 Years of Age – Excluding Cycles Where Any Use of Other Birth Control Method (BCM) Was Reported

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Completed Cycles	Pearl Index	95% Confidence Interval*
Sponsor	621	5	2177	600	1577	1.27	-
Reviewer	622	7	2178	600	1578	1.77	(0.71, 3.64)

Source: Table 6.2.1, page 71, Study PSE-301 report and the Statistical reviewer's listing.
* 95% confidence interval calculated by the Statistical Reviewer.

The Sponsor life table pregnancy rate using all completed cycles is 0.61% (95% C.I. from 0.19% to 1.90% - Table 7.1.1, page 76, Study PSE-301 report). The Reviewer life table pregnancy rate using all completed cycles is 0.63% (95% C.I. from 0.01% to 1.26%).

3.1.2 Study PSE-302 Results

Table 4.3 presents the Pearl Index results for Seasonique 10 μg in supportive study PSE-302 in all treated subjects 18-35 years of age for the Sponsor and Reviewer. The Sponsor and Reviewer report one pregnancy and a Pearl Index of 2.41.

Table 4.3
Study PSE-302: Results for Sponsor and Reviewer - Pearl Index Calculation of Treatment Failure Rates for Seasonique 10 μg: Completed Cycles Only – All Treated Subjects 18-35 Years of Age – Excluding Cycles Where Any Use of Other Birth Control Method (BCM) Was Reported

N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Completed Cycles	Pearl Index	95% Confidence Interval*
61	1	217	51	166	2.41	(0.06, 12.94)

Source: Table 6.2.1, page 77, Study PSE-302 report.
* 95% confidence interval calculated by the Statistical Reviewer.

The Sponsor reports a life table pregnancy rate using all completed cycles of 2.02% (95% C.I. from 0.29% to 13.5% - Table 7.1.1, page 83, Study PSE-302 report). The Reviewer reports a life table pregnancy rate using all completed cycles of 1.90% (95% C.I. from 0% to 5.60%).

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. The Sponsor did not provide data for statistical evaluation to support the 10 μg of EE for the last 7 days of the 91-day cycle. For additional information, reference the clinical review evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

There are no subgroup populations of interest in this submission.

5. CONCLUSIONS

From a statistical standpoint, the Sponsor has provided one study that is adequate for demonstrating the effectiveness of Seasonique 10 μg 91-day extended regimen oral contraceptive in the prevention of pregnancy.

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/s/

Sonia Castillo
6/30/05 02:44:27 PM
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Mike Welch
6/30/05 03:45:51 PM
BIOMETRICS
Concur with review.

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-840 (Serial 000)

Applicant: Duramed Pharmaceuticals, Inc.

Trade/Generic Name: Seasonique® (levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg and ethinyl estradiol tablets 0.01 mg)

Indication: The prevention of pregnancy

Date of Submission: October 21, 2004

Filing Date: December 20, 2004

User Fee Goal Date: August 19, 2005

Project Manager: Karen Kirchberg

Medical Reviewer: Ronald Orleans, M.D.

Comments: As of December 9, 2004, the Division is waiting for submission of requested analyses of the Pearl Index. Otherwise, this NDA is fileable from a statistical perspective.

Checklist for Fileability	**Remarks (NA if not applicable)**
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	EDR data present
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	NA

Reviewer: S. Castillo

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/s/

Sonia Castillo
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