CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

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 AND EVALUATION
Clinical Studies

NDA/Serial Number:	22-262 / 000
Drug Name:	Lo Seasonique (Levonorgestrel 0.1 mg/EE 0.02 mg + EE 0.01 mg) oral contraceptive
Indication(s):	Prevention of pregnancy
Applicant:	Duramed Pharmaceuticals, Inc.
Date(s):	Letter Date: December 26, 2007 PDUFA Date: October 24, 2008
Review Priority:	1S
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products
Clinical Team:	Ronald Orleans, M.D., Medical Reviewer Lisa Soule, M.D., Team Leader
Project Manager:	Kassandra Sherrod
Key Words:	Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Lo Seasonique 10 µg 91-day extended regimen oral contraceptive has demonstrated a Pearl Index of 2.94 (95% confidence interval is 2.07 to 4.06).

1.2 Background

The Sponsor has submitted one, multi-center, open label, uncontrolled, randomized, parallel-group study to demonstrate the safety and efficacy of Lo Seasonique oral contraceptive to prevent pregnancy, in sexually active women aged 18 to 35 years of childbearing potential over one year of use. Lo Seasonique 0.01 mg is a 91-day extended regimen oral contraceptive composed of 0.01 mg levonorgestrel (LNG) and 0.02 mg ethinyl estradiol (EE) for the first 84 days of a 91-day treatment cycle and 0.01 mg EE for the last 7 days of a 91-day treatment cycle. Lo Seasonique is a lower dose version of the currently marketed Seasonique (reference NDA 21-840), which is composed of 0.15 mg LNG and 0.03 mg EE taken for the first 84 days of the 91-day treatment cycle followed by 0.01 mg EE during the last 7 days of the 91-day treatment cycle.

The Sponsor's proposed indication is:

Lo Seasonique™ Tablets are indicated for the prevention of pregnancy in women.

1.3 Statistical Issues and Findings

There is one statistical issue with this submission: the Medical Reviewer has identified three additional pregnancies and they will be used to calculate the Pearl Index. Also, the three total cycles for one of the new identified pregnancies were not included in the Sponsor's Pearl Index calculation but will be used in my calculation.

Efficacy is based on calculation of the pregnancy rate using the Pearl Index in women aged 18 to 35 years. In this study, the Pearl Index for Lo Seasonique is 2.94 (95% C.I. from 2.07% to 4.06%).

2. INTRODUCTION

2.1 Overview

The Sponsor has submitted one, multi-center, open label, uncontrolled, randomized, parallel-group study (DR-PSE-309) designed to demonstrate the safety and efficacy of the 91-day extended regimen oral contraceptive Lo Seasonique in sexually active women aged 18 to 35 years for the prevention of pregnancy. Table 2.1 presents a brief summary of the study.

Table 2.1
Brief Summary of Clinical Study for Lo Seasonique

Study Number (No. of Centers / Country) Dates of Study Conduct	Treatment	Sample Size Enrolled (Treated)	Duration of Treatment	Design[1]
DR-PSE-309 (56 / U.S.) 6-17-05 to 6-8-07	Levonorgestrel (0.1 mg) /EE (0.02 mg) x 84 days, followed by EE 0.01 mg x 7 days	2235 (2185)	Four 91-day cycles	OL, R, MC, U

Source: Statistical reviewer's listing.
[1] OL = Open Label, R = Randomized, PG = Parallel Group, MC = Multicenter, U = Uncontrolled
[1] LNG = levonorgestrel, EE = ethinyl estradiol,

The Sponsor's proposed indication is:

Lo Seasonique™ Tablets are indicated for the prevention of pregnancy in women.

2.2 Data Sources

The study report and additional information for this study are submitted electronically. The submitted SAS data sets for the study are complete and well documented. These items are located in the Electronic Document Room at \\Fdswa150\nonectd\N22262\N_000 under the submission dated 12-26-2007.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Study DR-PSE-309 is a multi-center, open label, uncontrolled, randomized, parallel-group study conducted for a period of four 91-day cycles of Lo Seasonique oral contraceptive therapy. Sexually active women aged 18 to 40

years who satisfied the inclusion criteria, which included a negative urine pregnancy test and agreement to use the study oral contraceptive therapy as their only birth control method, were enrolled. Subjects took one tablet daily and entered data into a paper diary to record their daily study medication use, incidence of bleeding and/or spotting and any additional forms of contraception used. Subjects were followed for 30 days following completion of the study or early withdrawal or discontinuation for the occurrence of pregnancy.

The primary objectives of the study are to demonstrate the efficacy and safety of Lo Seasonique. The Pearl Index for subjects 18-35 years of age is the primary efficacy variable, which is calculated using all on treatment pregnancies in those women 18 to 35 years of age, completed cycles, and excluding any cycles where other birth control methods (BCM) were 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.

3.1.1 Overall Study Descriptive Statistics

Table 3.1 presents the number of randomized subjects and the disposition of treated subjects 18-35 years of age. The primary reason for study discontinuation is "lost to follow-up" (14.1%). Also, of the treated subjects aged 18-35 years, the mean age is 26.4 years and the majority of subjects are Caucasian (74.2%).

Table 3.1
Study DR-PSE-309: Randomization and Disposition of All Treated Subjects 18-35 Years of Age for Lo Seasonique

Number Randomized	2235
Number Treated (ITT)	2185
Treated, 18-35 Years of Age with at Least 1 Completed Cycle on Treatment n (%*)	1735 (79.4)
Discontinued n (%**)	644 (37.1)
Primary Reason for Discontinuation n (%**):	
Lost to Follow-up	244 (14.1)
Subject Request to be Withdrawn	149 (8.6)
Adverse Event	143 (8.2)
Non-compliant	53 (3.1)
Pregnant	30 (1.7)
Other	25 (1.4)

Source: Tables 3 and 6, pages 54 and 57, Study DR-PSE-309 report.
* With respect to number of treated subjects.
** With respect to number of treated subjects 18-35 years of age.

3.1.2 Efficacy Results

Table 3.2 presents the Pearl Index results for Lo Seasonique in all treated subjects 18-35 years of age for the Sponsor and Reviewer. The Sponsor reports 33 pregnancies and a Pearl Index of 2.70. The Reviewer reports 36 pregnancies and a Pearl Index of 2.94.

Table 3.2
Study DR-PSE-309: Results for Sponsor and Reviewer - Pearl Index Calculation of Treatment Failure Rates for Lo Seasonique: Completed 91-Day Cycles Only – All Treated Subjects 18-35 Years of Age – Excluding 91-Day Cycles Where Any Use of Another 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	1649	33	5461	572	4889	2.70	(1.86, 3.79)
Reviewer	1650	36	5464	572	4892	2.94	(2.07, 4.06)

Source: "Summary Table of Pearl Index Calculations, by Patient Cohort", page 9 of Study DR-PSE-309 Clinical Summary report and the Statistical reviewer's listing.

The clinical team requested that a 28-day cycle Pearl Index be reported. This Pearl Index based on 28-day cycle data, 36 pregnancies in 1729 subjects, and 17068 completed 28-day cycles where no other BCM was used is 2.74 (95% C.I. from 1.92 to 3.78).

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Lo Seasonique 10 µg 91-day extended regimen oral contraceptive has demonstrated a Pearl Index of 2.94 (95% confidence interval is 2.07 to 4.06).

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The Sponsor life table pregnancy rate in all treated subjects 18-35 years of age using all completed 91-day cycles and 33 pregnancies is 2.19% (95% C.I. from 1.53% to 3.14% - Table 27, page 74, Study DRE-PSE-309 report). The Reviewer life table pregnancy rate in all treated subjects 18-35 years of age using all completed 91-day cycles and 36 pregnancies is 3.2% (95% C.I. from 1.2% to 5.2%).

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. 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 adequate study that provides evidence of the effectiveness of Lo Seasonique 91-day extended regimen oral contraceptive in the prevention of pregnancy.

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/s/

Sonia Castillo
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Mahboob Sobhan
6/5/2008 04:28:08 PM
BIOMETRICS

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA: 22-262 **Applicant:** Duramed Pharmaceuticals, Inc. **Submission Date:** 12/26/2007
Drug Name: Lo Seasonique **Indications:** Prevention of pregnancy **45 day Meeting Date:** 2/7/2008
Medical Officer: Ron Orleans, M.D., DRUP **Project Manager:** Kassandra Sherrod

A: Summary

This filing review will determine whether the format and content of the safety and efficacy database for this NDA is sufficiently complete for substantive statistical review as per study protocol. The data from one Phase 3 study (Study DR-PSE-309) is considered pivotal to support the pregnancy prevention indication for Lo Seasonique (Levonorgestrel/Ethinyl estradiol (EE) 0.1 mg/0.02 mg and EE 0.01mg). This is a randomized, open-label, multicenter study conducted for a period of four 91-day cycles. The primary efficacy assessment was the pregnancy rate over the four 91-day cycles based on the Pearl Index in those women 18 to 35 years of age, who completed at least one 91-day cycle of treatment and using only those cycles where no other birth control method was used (PITT population).

Based on Applicant's PITT analysis, the pregnancy rate based on the Pearl index is 2.44. The Applicant's submission includes all the data sets necessary for statistical review.

Brief Summary of Clinical Study for Lo Seasonique

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Source: Statistical reviewer's listing.
[1] OL = Open Label, R = Randomized, PG = Parallel Group, MC = Multicenter, U = Uncontrolled

B: Conclusion

After preliminary review of the submission of the following checklist items, no refuse-to-file deficiencies are identified. The Applicant provided the required information and all data sets are accessible to perform statistical evaluation, therefore, this NDA is fileable from a statistical perspective.

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			No ISS or ISE Only 1 study
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			X	All female, majority white
Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.s			X	
Appropriate references for novel statistical methodology are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	Only 1 study
Investigation of dropout effect on statistical analyses as described by applicant appears adequate.	X			

Sonia Castillo 2/7/2008
Reviewing Statistician, Div. of Biometrics 3 Date

Mahboob Sobhan 2/7/2008
Supervisor/Team Leader, Div. of Biometrics 3 Date

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/s/

Sonia Castillo
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Mahboob Sobhan
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