CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-262

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-262
Submission Code	000
Letter Date	December 26, 2007
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PDUFA Goal Date	October 24, 2008
Reviewer Name	Ronald J. Orleans, M.D.
Review Completion Date	October 23, 2008
Established Name	Levonorgestrel/ethinyl estradiol; ethinyl estradiol
(Proposed) Trade Name	LoSeasonique™
Therapeutic Class	Oral contraceptive
Applicant	Duramed Research, Inc.
Priority Designation	S
Formulation	Eighty-four levonorgestrel 0.1 mg/ethinyl estradiol 0.02 mg tablets followed by 7 ethinyl estradiol 0.01 mg tablets continuously
Dosing Regimen	One tablet daily
Indication	Prevention of pregnancy
Intended Population	Women of reproductive age at risk for pregnancy who desire contraception

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of Lo Seasonique™ for prevention of pregnancy is recommended based on Duramed Research, Inc. (the Applicant) having demonstrated an acceptable Pearl Index and an acceptable safety profile for this product.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Standard post-marketing surveillance (AERS) is recommended to further monitor the efficacy and safety of Lo Seasonique. No specific risk management steps are recommended.

1.2.2 Required Phase 4 Commitments

There are no required phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no other phase 4 requests of the Applicant.

1.3 Summary of Clinical Finding

1.3.1 Brief Overview of Clinical Program

Duramed Research, Inc. has proposed a new extended-cycle oral contraceptive (OC) to be approved for the indication of prevention of pregnancy. To seek approval for this regimen, the Applicant has submitted NDA 22-262 under Section 505(b)(1). The NDA application consists of a single multicenter, one-year, open-label clinical trial, DR-PSE-309, which was conducted under IND 63,735. This primary study of 2,185 women had a single arm, so did not utilize a comparator oral contraceptive. The study was designed to provide adequate evidence supporting the efficacy and overall safety of Lo Seasonique. In addition to the primary clinical trial data from Study DR-PSE-309, Duramed also submitted data obtained from Study 99027, which was a randomized open label, two-way crossover, bioequivalence study. This study assessed the bioequivalence of levonorgestrel/ethinyl estradiol combination tablets of Lessina® compared with Levlite® following a single dose of LNG 0.30 mg/EE 0.06 mg in healthy females under fasting conditions.

1.3.2 Efficacy

Efficacy was based on the ability of Lo Seasonique to prevent pregnancy in the single phase 3 clinical trial submitted to the NDA. This was calculated by the Pearl Index (PI) using all "on-drug" pregnancies. On-drug pregnancies were defined as those pregnancies for which conception occurred on or after the date of first taking the study drug and extending through the 14 days following the last dose of the active LNG/EE combination tablet, which typically occurred on day 84 of a completed cycle. Conceptions that occurred 15 days or more past the last dose of the active LNG/EE combination tablets were not considered as "on-drug" pregnancies.

The most conservative approach to calculate the Pearl Index was utilized. The PI was derived from the Pregnancy Intent to Treat cohort (PITT), which consisted of all women ages 18-35 who completed at least one full cycle of therapy (N=1,735). Although the "cycle length" for extended-cycle OCs is 91 or 365 days, the Division also evaluates pregnancy and bleeding outcomes based on 28-day cycles, as is done for typical OC regimens. All 28-day cycles where additional back-up methods of birth control (including condoms) were used and all incomplete 28-day cycles (except those in which conception occurred) were excluded from the denominator used in the PI calculation. This left a sub-cohort of 1,729 subjects who used the drug over 17,068 completed 28-day cycles.

As determined by the Medical Reviewer, 36 on-drug pregnancies occurred during the study in the PITT population. Based on these 36 pregnancies, which occurred over 17,068 completed 28-day cycles where no other back-up method of birth control was used, the Pearl Index for Lo Seasonique was calculated by the FDA Statistician to be 2.74 (95% CI: 1.92, 3.78) per 100 women-years of use. A minimum of 10,000 28-day cycles are usually studied for new non-new molecular entity (NME) OCs, therefore the 17,068 28-day cycles studied in this NDA are considered sufficient for determining efficacy. The Pearl Index of 2.74 is acceptable to support the efficacy of Lo Seasonique.

1.3.3 Safety

The safety database for Study DR-PSE-309 consists of the 2,185 subjects who received at least one dose of study medication (Safety cohort).

Duramed did not submit any new nonclinical pharmacokinetic or toxicology studies in support of the current application. The Applicant concluded (and the Pharm Tox reviewer agreed) that the safety of Lo Seasonique could be adequately demonstrated without additional nonclinical studies because sufficient data relating to the safety of LNG/EE already existed, and that this data also supports the safety of the lower dosing regimen (LNG 100 mcg/EE 20 mcg) found in Lo Seasonique.

A total of 1,249 subjects completed the one-year study. This exceeds the Division's required subject exposure of 200 women for at least one year.

No new safety concerns have arisen from the Lo Seasonique primary trial. No deaths or venous thromboembolic events (VTEs) occurred during this trial. The serious adverse events (SAEs) possibly related to study drug that occurred during the trial were comparable to those known to be associated with OC use. Approximately 936 (43%) of the subjects discontinued the study prematurely. Of these, 253 (11.6%) discontinued because of an adverse event. The most common adverse events leading to study discontinuation were bleeding and/or spotting, headache, nausea, and mood swings. The clinical and laboratory adverse events reported in the study were similar to those observed in trials involving other extended cycle OCs. The most commonly reported adverse events possibly related to the study drug were headache (33.4%), irregular and/or heavy uterine bleeding (13%) and dysmenorrhea (11.3%).

Review of the safety data provided in this NDA supports the safety of Lo Seasonique when used for prevention of pregnancy.

1.3.4 Dosing Regimen and Administration

Active extended cycle combination oral contraceptive tablets are given for 84 days followed by seven days of inactive (placebo) tablets. This regimen was previously approved with Seasonale and Seasonique. With Lo Seasonique, the placebo tablets taken daily on days 85-91 are replaced with EE 10 mcg tablets.

1.3.5 Drug-Drug Interactions

No analyses of drug-drug or drug-disease interactions were performed for this product.

1.3.6 Special Populations

Combination OCs are intended for the population of women at risk for pregnancy.
No formal pharmacokinetic studies of Lo Seasonique were performed in different racial groups. However, there is no evidence in the medical literature that the safety or efficacy of OCs differ with regard to race.

No formal studies were done to evaluate the effect of hepatic or renal disease on the metabolism of Lo Seasonique. The fact that steroid hormones may be poorly metabolized in patients with impaired liver function is already part of class labeling for OCs.

The Applicant has requested a full waiver of all pediatric studies because, according to class labeling, the safety and efficacy of LNG/EE combination tablets have been established in all women of reproductive age. The safety and efficacy profile of OCs is expected to be the same for post pubertal adolescent females less than 18 years of age as it is for females older than 18 years of age. A waiver is therefore recommended.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established drug name combination for this product is levonorgestrel (LNG) and ethinyl estradiol (EE). The chemical name for LNG is 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, (-)-. The chemical name for EE is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. The proposed trade name is LoSeasonique™ (hereafter referred to as Lo Seasonique). Lo Seasonique is a 91-day "low dose" extended cycle oral contraceptive (OC) containing 84 combination tablets of LNG 100 mcg and EE 20 mcg, followed by seven tablets of EE 10 mcg monotherapy. The product is intended for women of reproductive age at risk for pregnancy and who desire contraception.

2.2 Currently Available Treatment for Indications

Combination 28-day OC products containing LNG and EE have been marketed for decades worldwide. When OCs were first introduced, the dosage regimen was designed to induce withdrawal bleeding every 28 days. The 28-day regimen (21 days of active tablets followed by 7 days of placebo tablets) attempted to imitate as closely as possible the length of the normal menstrual cycle to make the pill more acceptable. For some women, the presence of withdrawal bleeding each month is reassuring for general health reasons and also reassuring as an indication that they are not pregnant. For other women, the prospect of eliminating monthly periods and the possible mitigation of perimenstrual symptoms is more important than the reassurance of monthly withdrawal periods.

Off-label extended use of numerous types of OCs has been employed clinically for many years. Clinicians have at times advised patients to omit placebo pills in their OC regimens and extend the active pills for either medical reasons (e.g., for treatment of symptoms of endometriosis) or social reasons (e.g., wishing to avoid menses during a vacation).

Mircette® (NDA 20-713) was the first approved combination OC to use a shortened placebo interval. The Mircette regimen consists of desogestrel 150 mcg/ EE 20 mcg for 21 days followed by placebo tablets for two days and then followed by EE 10 mcg for five days. Organon proposed that the substitution of EE 10 mcg for placebo pills on days 24 to 28 in Mircette would improve efficacy and cycle control, however studies failed to show that the addition of EE on days 24 to 28 improved follicular suppression or cycle control compared with continuing placebo pills during this time. Mircette's unique regimen was found upon review to offer no advantages over existing regimens but it showed adequate efficacy and safety and was approved on April 22, 1998.

The first "extended-cycle" OC approved by the FDA was Seasonale® (NDA 21-544). Seasonale was approved on September 5, 2003 and is a combination OC that contains LNG 150 mcg and EE 30 mcg in each active tablet. The dosing regimen is one active tablet daily for 84 days followed by seven inactive (placebo) tablets (a 91-day or "extended" dosing cycle). The primary

benefit of Seasonale, in addition to contraception, is to reduce the number of scheduled bleeds to four per year in contrast to 13 scheduled withdrawal bleeds per year as occurs with a conventional 28-day cycle OC.

Seasonique® (NDA 21-840) was the second extended-cycle OC approved by the FDA (May 25, 2006). Seasonique, like Seasonale, is a 91-day extended regimen combination OC with LNG 150 mcg/EE 30 mcg, administered orally for 84 days, followed by 7 days of EE 10 mcg monotherapy substituted for the 7 day placebo period utilized in Seasonale®. No unusual safety issues were observed in the primary clinical trials supporting the approval of either Seasonale or Seasonique.

Medical Reviewer's Comment

- *Although the substitution of EE 10 mcg for placebo on days 85-91 of each extended cycle has no proven benefit for patients, the Applicant believes that the addition of EE during the pill-free week of the extended cycle regimen may reduce ovarian follicular activity which may lead to a lower risk of escape ovulation and unintended pregnancy. This has not been systematically evaluated.*

Lybrel® (NDA 21-864) was approved by the FDA in May of 2007. Lybrel is a 365-day extended cycle combination OC which does not utilize a hormone-free interval. The dosage regimen is one tablet containing LNG 90 mcg/EE 20 mcg given daily.

In NDA 21-262, Duramed Research, Inc. has studied a new extended-cycle, low-dose OC regimen for the prevention of pregnancy, DP3-Lo 84/10 (Lo Seasonique), containing LNG 100 mcg and EE 20 mcg as a combination tablet taken for 84 days followed by EE 10 mcg alone as monotherapy for 7 days. The active combination of LNG/EE in a 5:1 ratio that is taken daily on days 1-84 is the same active drug component of currently marketed "low-dose" OCs such as Alesse and Levlite.

Lo Seasonique is a somewhat unique OC because it combines the low dose LNG/EE active dose regimen with the EE 10 mcg monotherapy given during days 85-91 of the cycle.

2.3 Availability of Proposed Active Ingredient in the United States

The first OC approved for marketing by the FDA was Enovid (mestranol 150 mcg and norethynodrel 9.85 mg) which was approved in 1960. EE has been widely used as the estrogenic component of numerous combination OCs in the US since 1964. LNG was first approved as the progestogen in a combination OC with EE in 1982. Several 28 day LNG/EE combination OCs are currently being marketed. These include Levlite®, Alesse®, Nordette® , and Triphasil®. Extended cycle OCs which contain LNG/EE include Seasonale®, Seasonique®, and Lybrel®. The combination of LNG 100 mcg/EE 20 mcg used in Lo Seasonique is the same dosage strength as that contained in each active tablet of Alesse (NDA 20-683), which was approved on 1997 and Levlite (NDA 20-860), approved in 1998. This LNG/EE dosage combination is also found in generic versions (Aviane approved in 2001 and Lessina 21/28 approved in 2002).

There are approximately 21 different brands of combination oral contraceptives containing LNG/EE currently approved in the United States (See Appendix Section 10).

Medical Reviewer's Comment

- *LNG and EE in the doses proposed have been used safely in oral contraceptives for a long period of time.*

2.4 Important Issues With Pharmacologically Related Products

Important issues with OCs revolve around contraceptive efficacy and adverse events. Efficacy and safety have been well categorized for this pharmacologic class as a whole since its initiation in the 1960s. The most significant adverse events are thromboembolic and cardiovascular. Serious adverse events have decreased with reduction in daily doses of ethinyl estradiol and progestins.

Currently available 28-day OCs containing 20 mcg EE have been shown in clinical studies to be highly effective and safe, with fewer side effects than higher dose pills. The Applicant believes that escape ovulation may be more common as the doses of LNG/EE decrease, such as in the proposed Lo Seasonique formulation, so that minimizing the potential for this response by the addition of low doses of EE during the seven day interval between cycles may be of value.

Medical Reviewer's Comment

- *The clinical benefit of substituting low dose EE for placebo has never been demonstrated in a well controlled phase 3 clinical trial. However, the substitution has no adverse effect on the safety and efficacy of the product when it is used as indicated for the prevention of pregnancy.*

2.5 Presubmission Regulatory Activity

Seasonale® was the first 91-day extended cycle OC regimen approved for the prevention of pregnancy by the U.S. Food and Drug Administration (FDA). Seasonale (NDA 21-544) consists of 84 days LNG 150 mcg/EE 30 mcg followed by 7 days of placebo tablets. The calculated Pearl Index for this product was **1.98**. The primary study that was used to support the approval of NDA 21-544 (IND 60,399, Study SEA-301) also included an extended cycle lower dose arm containing LNG 100 mcg/EE 20 mcg followed by 7 days of placebo. (b) (4) [redacted] Seasonale, as mentioned above, was approved for the indication of prevention of pregnancy on September 5, 2003.

In 2006, Seasonique™ became the second extended cycle OC approved for marketing for the prevention of pregnancy by the FDA. Seasonique, like Seasonale, is a 91-day extended cycle regimen, with the combination LNG 150 mcg/EE 30 mcg tablet administered orally for 84 days. However, instead of the 7 days of placebo tablets found in Seasonale, Seasonique substitutes 7 days of EE 10 mcg monotherapy for the placebo tablet. The calculated Pearl Index for this

product was **1.77**. Although no additional benefit was demonstrated with the use of this additional EE 10 mcg instead of placebo, no unusual safety issues were observed, so the drug merited approval.

(b) (4)

Medical Reviewer's Comment

- *The oral contraceptive with the highest Pearl Index approved by this Division for the indication of prevention of pregnancy is Ortho TriCyclen Lo which has a Pearl Index of 2.67.*

On June 24, 2005, the Applicant submitted a new drug application under section 505(b)(1) for Seasonale Lo (NDA 21-921) for the prevention of pregnancy. (b) (4)

(b) (4)

(b) (4) The application was withdrawn prior to an action being taken because of these review issues.

In this current NDA submission, Duramed Research, Inc. has again studied an extended 91-day cycle, low-dose, oral contraceptive regimen, Lo Seasonique. The study (Protocol DR-PSE-309) also collected information on the incidence and severity of bleeding and spotting. (b) (4)

Protocol DR-PSE-309 was initially submitted by the Applicant on June 6, 2005 under IND 63,735 (S-032). IND 63,735 (S-081) dated July 20, 2007 contained the Statistical Analysis Plan for the protocol and was reviewed by the FDA statistician. In a letter dated December 20, 2007, (Serial No. 090), the Applicant responded to the Division's comments regarding the Statistical Plan for DR-PSE-309, agreeing with the Division's recommendations, which included:

- Both Pearl Index calculations and Life Table estimates will include analyses based on the population 18 to 35 years of age who complete at least one cycle of treatment and who used no other form of additional contraception (including condoms).

- For primary efficacy purposes, "on-drug" pregnancies will be defined as occurring during the use of study drug or within 14 days after taking the last active dose of study drug.

2.6 Other Relevant Background Information

NDA 21-262 was submitted on December 26, 2007 for Division review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The formulation of Lo Seasonique™ was based on (b) (4) tablets with the same core tablet composition. (b) (4) ; generic product Lessina® tablets (ANDA 75-803), an FDA approved product with the same core tablet composition. The only difference between these formulations is the color of the cosmetic film coat. The formulation of the EE 10 mcg tablets is identical to the EE 10 mcg tablets used in the marketed product Seasonique™ (LNG 150 mcg//EE 30 mcg tablets and EE 10 mcg tablets). Hence minimal developmental work was required for the Lo Seasonique™ tablets.

(b) (4)

Medical Reviewer's Comments

- *There are no product microbiology issues.*
- *The Chemistry reviewer has determined that the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product and that from a CMC perspective, the NDA is recommended for approval.*
- *Duramed Pharmaceuticals, Inc. believes that it is in compliance with all applicable Federal, State and Local environmental laws and has requested that environmental assessment not be required with the application. The Chemistry reviewer agrees that environmental assessment need not be required of the Applicant.*
- *The following deficiencies were initially identified by the FDA reviewing chemist:*
  - *Confirm the Master Batch Formula for the manufacture of each type of tablet used in clinical and/or stability studies.*
  - *Provide additional stability data when it is available.*
  - *Indicate the presence or absence of an overage for either of the active pharmaceutical ingredients (levonorgestrel, ethinyl estradiol).*
  - *Submit a Letter of Authorization for DMF* (b) (4)
- *These deficiencies were satisfactorily resolved by the Applicant so that, from a CMC standpoint, the application merits approval.*

3.2 Animal Pharmacology/Toxicology

No pharmacology/toxicology studies were conducted or submitted by the Applicant. . The safety of the drug product is supported by reference to approved combination oral contraceptives containing levonorgestrel and ethinyl estradiol.

Medical Reviewer's Comments

- *The Applicant did not believe it necessary to submit additional nonclinical studies to the NDA because sufficient data already exists supporting the safety of Seasonale and Seasonique and that these data also support the safety of the Lo Seasonique dosing regimen.*
- *As stated in the Pharmacology/Toxicology Review, Dr. Alex Jordan agreed that no new pharmacology, toxicology or pharmacokinetic/toxicokinetic studies were necessary to support this NDA. He concluded that there were no significant review issues regarding Pharmacology/Toxicology.*

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Documents consulted in this review include:

- Paper and electronic submissions for NDA 21-262
- Additional information requests of the Applicant including:
    - Chemistry, Manufacturing and Controls request for an Environmental Assessment and other CMC information. Information received from the Applicant on 03/27/08 and 06/06/08.
    - Information regarding three pregnancies which the Division believes are "on-drug" pregnancies. Information received from the Applicant on 06/20/08.
    - Analysis of unscheduled bleeding/spotting based on all subjects who received at least one dose of study drug (safety cohort). Information received from the Applicant on 09/05/2008.
    - A table showing the number of on-drug pregnancies in each decile by baseline weight. Information received from the Applicant on 06/03/2008.
    - A bar graph representing the percentage of subjects who bled for 7 or more days and for 20 or more days during each 91-day cycle of treatment. Information received from the Applicant on 07/25/08.
- Medical Officer's Review of NDAs 21-840 (Seasonique), 21-921 (Lo Seasonale), and 21-544 (Seasonale)
- Medical Officer's Review of IND 63,735
- Consultation reports from other disciplines
- PubMed searches and journal reviews

4.2 Table of Clinical Studies

Table 1 Overview of Primary Clinical Trial, DR-PSE-309

Phase 3 Study: DR-PSE-309	Study Design	Number of Subjects	Study Duration	Study Drug
-First subject enrolled: 6/17/2005 -Last subject completed: 11/30/2007	-Open-label -Single arm	-2235 enrolled -Safety cohort (n=2185)* -Intent-to-treat cohort (n=1950)** -Pregnancy intent-to-treat cohort (n=1735)***	-Four 91-day cycles	-DP3-Lo 84/10: 84 days of LNG/EE 100 mcg/20 mcg followed by 7 days of EE 10 mcg

*Safety Cohort: All subjects who received at least one dose of study drug, whether or not the subjects ever returned for any post-baseline study visit.
**ITT Cohort: All subjects who were randomized to treatment and completed at least one cycle (84 days) of study medication.
***PITT Cohort: All treated subjects between 18 and 35 years of age who completed at least one cycle (84 days) of treatment.
Source: NDA 22-262, Adapted from the Clinical Study Report (CSR)

4.3 Review Strategy

In order to evaluate the safety and efficacy of Lo Seasonique, the following items were reviewed:

- Data from the single, phase 3 clinical study submitted to the NDA (Study DR-PSE-309).
- Presubmission meeting minutes between the Applicant and the Division.
- Original primary study protocol submitted under IND 63,735 (Serial No. 032) submitted June 6, 2005.
- Applicant's original Statistical Analysis Plan (Serial No. 081), submitted July 16, 2007.
- Response to Division comments on PSE-309 Statistical Analysis Plan (Serial No. 090), dated December 20, 2007.
- Consultation from the Division of Medication Error Prevention and Analysis (DMEPA) regarding the requested proprietary name.
- Consultation from the Division of Drug Marketing, Advertising and Communication (DDMAC) regarding review of the proposed Package Insert (PI) for potential marketing and advertising implications.
- Consultation from the Division of Risk Management (DRISK) regarding the Applicant's communication of appropriate risk information in the Patient Package Insert (PPI).

Medical Reviewer's Comments

- *DDMAC has reviewed the proposed PI and had no comments regarding possible future promotional implications.*
- *DRISK concluded that the Applicant's proposed PPI was not consistent with the format and language in the March 2004, Draft Guidance: Guidance for Industry: Labeling for Combined Oral Contraceptives. (This guidance document, however, is no longer being used for labeling; instead a new draft guidance under internal review is forming the basis of labeling recommendations.) Several suggestions were made in the consultation response for revising the Brief Summary and the Detailed Patient Summary within the PPI.*
- *DMEPA has reviewed the proprietary name for this product "Lo Seasonique." There were no objections to the proposed name. They commented that the position of the prefix Lo immediately preceding rather than following the root name may help in distinguishing Lo Seasonique from Seasonique. DMEPA suggested, however, that eliminating the space between the modifier, "Lo", and the root name, Seasonique, may reduce the possibility that the two parts of the name will be separated and that the "Lo" would not be misinterpreted as a net quantity, since Lo can resemble the number "10." The Applicant has agreed to remove the space.*

4.4 Data Quality and Integrity

Methods used to evaluate data quality and integrity include:

- Review of possible bias based on financial ties
- Seeking source documentation for efficacy analysis compliance with Good Clinical Practices

Medical Reviewer's Comment

- *The Medical Reviewer determined that site inspections by the Division of Scientific Investigations (DSI) were not warranted. Many of the sites were recognized to have participated in other OC investigations or have been previously inspected.*

4.5 Compliance with Good Clinical Practices

The study was designed and conducted in accordance with the regulations pertaining to Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki (revised, South Africa, 1996).

4.6 Financial Disclosures

In Study (b) (6) financial disclosure information was obtained from all participating investigators with the exception of one sub-investigator at study Site (b) (6) ,who was mistakenly added to the Form FDA 1572. (b) (6) s name was removed as a sub-investigator and was not involved with the study. A new SF 1572 was filed by the site.

Only three investigators disclosed financial arrangements with the Applicant:

- (b) (6) . (Principal Investigator at Site (b) (6), which enrolled (b) (6) subjects) received an honoraria "not exceeding $15,000.00."
- (b) (6) H (Principal Investigator at Site (b) (6), which enrolled (b) (6) was paid $1000.00 by (b) (6) for attending speaker training for hormone therapy.
- (b) (6) . (Principal Investigator at Site (b) (6), which enrolled (b) subjects) is "paid less than $10,000.00 annually" to provide consultation and lecture services to the Applicant. In addition, he is the recipient of an ongoing clinical trial grant from the Applicant.

Medical Reviewer's Comments

- (b) (6) *site enrolled (b) (6) subjects. No protocol deviations were reported from the site.* (b) (6) *subjects at his site withdrew from the study.* (b) (6) *of these subjects discontinued due to adverse events. A total of (b) serious adverse events and (b) (6) were reported by the site. A general review of these and other data submitted from this site did not provide evidence of investigator bias.*
- *Many sites enrolled a similar number of subjects. Site 10 enrolled approximately 179 subjects.*

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The active combination LNG/EE Lo Seasonique tablet is the same as that of Lessina® (ANDA 75-803 approved on 5/20/2002). The manufacturing process, and formulation are identical. The EE 0.01 mg tablets are the same tablets found in the marketed Seasonique® formulation. The Lo Seasonique clinical trial was conducted using the to-be-marketed formulation.

A bioequivalence study (Study 99027) was submitted by the Applicant to assess the bioequivalence of LNG/EE combination tablets of Lessina compared with Levlite® following a single dose of LNG 0.30 mg/EE 0.06 mg (3 tablet dose) in healthy females under fasting conditions. A single dose characterization was done.

Medical Reviewer's Comments

- *The distribution, metabolism and excretion profiles of Lessina and Seasonique are relied upon for labeling of Lo Seasonique, and single dose PK data were provided to characterize absorption.*
- *Based on the data obtained from the bioequivalence study submitted for review (Study 99027), the Clin Pharm reviewer has determined that the plasma PK parameters of LNG and EE following a single dose of Lo Seasonique were adequately characterized, and that (Lessina) was bioequivalent to the reference (Levlite) under fasting conditions.*
- *In the opinion of the Clin Pharm reviewer, the clinical pharmacology data submitted to support this NDA are acceptable and he has recommended approval.*

5.2 Pharmacodynamics

There were no pharmacodynamic studies requested or submitted for this NDA.

5.3 Exposure-Response Relationships

There are no significant review issues with Exposure-Response relationships. No measurements of study drug concentration were made during the safety and efficacy study.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The claimed indication for Lo Seasonique™ is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. The Applicant has submitted one primary, phase 3, one year clinical trial in support of this indication.

6.1.1 Methods

DR-PSE-309 was a prospective, multicenter, non-comparative, open-label study designed to demonstrate the efficacy and safety of the 91-day low-dose, combination OC regimen Lo Seasonique (84 days LNG 100 mcg/EE 20 mcg combination tablets followed by seven days of EE 10 mcg tablets), taken for up to four 91-day cycles, or one year, in women desiring pregnancy prevention.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was evaluated from the overall pregnancy rate, calculated by the Pearl Index (PI), using all "on-drug" pregnancies. The PI is defined as the annualized estimated rate of pregnancy per 100 women-years of exposure. Pregnancy was defined as a positive pregnancy test verified by the study staff. On-drug pregnancies are those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than

14 days after the date of the last dose of LNG/EE combination oral contraceptive therapy (typically Day 84 of the 91-day cycle).

- Pearl Index = $\frac{(100) \times (\text{number of pregnancies}) \times (13 \text{ cycles/year})}{(\text{total number of 28-day cycles completed})}$

The cohort used for the primary analysis was the Pregnancy Intent-to-Treat cohort (PITT), which consisted of all subjects between the ages of 18 and 35 at the initiation of study medication and who completed at least one 84-day cycle of study medication. However, an incomplete cycle in which a subject became pregnant was considered a complete cycle for all pregnancy calculations obtained by the above PI formula. Thus, if a patient conceived shortly after initiating study drug, that entire first cycle was included in the PI calculation. All 28-day cycles where additional methods of contraception were used (including condoms) were excluded from the Pearl Index calculation, except those in which a pregnancy occurred.

An alternative PI calculation can also be based on 91-day cycles. Calculation based on 91-day cycles would result in a change in the numerator from 13 to 4 cycles per year and a change in the denominator to the total number of 91-day cycles completed instead of 28-day cycles completed.

Medical Reviewer's Comment

- *The Division has used the above PI calculation with previous extended cycle oral contraception products; i.e., all treated patients 18-35 years of age who completed at least one 28-day cycle of study medication and excluding all 28-day cycles where any other birth control method (including condom) was used.*

Life Table Analysis

The cumulative pregnancy rate on a cycle-by-cycle basis was also estimated using a life table analysis. Cumulative pregnancy rates at 52 weeks were estimated using the life table method and 13-week (91 day) intervals. Unknown conception dates were estimated as the midpoint between the date of the last known negative pregnancy test and the date of the positive pregnancy test for the life table analysis.

Life tables were created for the following cohorts:

- Subjects between the ages of 18 and 35 who completed at least one cycle of treatment (PITT)
- The subset of the PITT cohort deemed to be compliant with study medication ("Compliant-Use") on a subject level, i.e., all of their cycles were considered compliant.

Medical Reviewer's Comment

- *In the life table analysis, exclusion of individual cycles from the subject's total would have led to a non-continuous time frame. In order to retain an uninterrupted time interval of participation for each subject, no individual cycles were removed. Therefore,*

the PITT Cohort excluding cycles where another form of birth control was used cannot be represented by the life table method.

6.1.3 Study Design

DR-PSE-309 (Primary Clinical Trial)

This primary phase 3 clinical trial for contraceptive effectiveness and safety is entitled: "A Multi-Center, Open-Label Study to Evaluate the Efficacy and Safety of an Extended Cycle, Low Dose, Combination Oral Contraceptive Regimen, Dp3-Lo 84/10, which Utilizes Ethinyl Estradiol during the Seven Day Interval between each 84-Day Cycle Of Combination Therapy for the Prevention of Pregnancy in Women." The protocol number for this trial is DR-PSE-309.

The trial utilized multiple investigators across 57 centers (56 centers enrolled subjects). All centers were in the US. The first subject was enrolled on 6/17/2005 and the last subject was completed on 6/8/2007. This multicenter, open-label study had only one treatment arm, so that every subject enrolled who took study drug received Lo Seasonique.

In the DR-PSE-309 trial, a total of 2,235 sexually active women of childbearing potential (ages 18 to 40) were enrolled and 2,185 subjects were treated, with 1,249 subjects completing four 91-day cycles of treatment. Total drug exposure was 6,442 91-day cycles or 20,937 28-day cycles.

Of the 2,235 enrolled subjects, 1,735 were in the PITT cohort (which was the principal cohort studied regarding the prevention of pregnancy and consisted of subjects between the ages of 18 and 35 years with at least one complete cycle on treatment), 1,950 in the ITT cohort (all subjects who were randomized to treatment and completed at least one extended cycle of study medication), and 2,185 were in the safety cohort (all subjects who received at least one dose of study medication). The overall study duration for each subject was approximately 14 months, which included a screening period of approximately four weeks, an open-label treatment period of one year (four 91-day extended cycles), and a four-week post-treatment period. The primary objective of this study was to demonstrate the efficacy and safety of Lo Seasonique over the course of one year in sexually active women, 18-35 years of age, who desired pregnancy prevention.

Subject Disposition
Of the 2,235 subjects enrolled, 2,185 (97.8%) received at least one dose of study medication. Of these 2,185 subjects who started treatment, a total of 1,950 (89.2%) completed at least one 91-day cycle of study medication.

Table 2 summarizes the number of enrolled subjects by treatment group included in each of the subject cohorts.

Table 2 Subject Cohorts

	N (% of Enrolled)
Screened	2,968
Enrolled and Randomized	2,235
All Subjects Treated with at Least One Dose of Study Drug (Safety Cohort)	2,185 (97.8%)
All Subjects Treated for at Least One Complete Cycle (ITT Cohort) ITT cohort < 90 kg	1,950 (87.2%) 1,651 (73.9%)
All Subjects 18-35 Years of Age Treated for at Least One Complete Cycle (PITT Cohort)) PITT Cohort < 90 kg PITT Cohort Compliant Use Only	1,735 (77.6%) 1,466 (65.6%) 1,685 (75.4%)

Source: NDA 22-262, CSR, Adapted from Table 3, Page 54

Protocol Amendments

The issue date of Protocol DR-PSE-309 under IND 63,735 was April 6, 2005. Two protocol amendments were made during the study.

Amendment #1 was issued on April 25, 2005. This Amendment contained no major substantive changes to the protocol. Amendment #2 was issued on June 3, 2005 and was an administrative amendment to revise packaging of the study drug.

A few changes in the planned analyses were made outside the protocol. The PITT cohort, which by definition required complete cycles of treatment for inclusion, was modified to include subjects who became pregnant during the first cycle of treatment, even if the cycle was not complete. These subjects were not included in the ITT cohort because they did not complete one cycle on treatment, but for the purposes of analyzing pregnancy rate, they were included in the PITT cohort.

Inclusion Criteria

1. Sexually active women (age 18 through 40 at the time of the screening visit) who were at risk for pregnancy and understood and comprehended the English language;
2. Capable of giving and willing to give informed consent;
3. Agreed to routinely use study oral contraceptive therapy as their only birth control method. (Another non-hormonal birth control method [such as condom, spermicide, foam, or contraceptive sponge] must have been used as a back up for the first 7 days of study medication use and in situations where two or more pills in a row were missed.) When intermittent therapies with drugs known to interact with oral contraceptives were initiated, another non-hormonal birth control method was to be used for the entire time the subject received the therapy and for a minimum of 7 days following discontinuation of the prohibited medication;
4. No contraindication to oral contraceptives;

5. For all subjects not using extended cycle contraception, subjects must have had a history of regular (approximately monthly) spontaneous menstrual cycles, or withdrawal bleeding episodes, for the 3-month period preceding the Screening Visit;
6. For subjects using extended cycle contraception, subjects must have completed a minimum of one extended cycle, including a spontaneous or withdrawal bleed prior to beginning the extended cycle and a withdrawal bleed prior to completion of the cycle immediately preceding study entry.

Medical Reviewer's Comment

- *The inclusion criteria are similar to those found in other OC studies and are acceptable.*

Exclusion Criteria

1. Any condition (history or presence of) which contraindicates the use of combination oral contraceptives, including:
    - Thrombophlebitis or thromboembolic disorders; known or suspected clotting disorders; thrombogenic valvulopathies or rhythm disorders;
    - Cerebrovascular or coronary artery disease or myocardial infarction;
    - Diabetes mellitus;
    - Migraine headaches with focal, neurological symptoms;
    - Chronic renal disease;
    - Uncontrolled or untreated hypertension (systolic BP ≥ 140 mmHg or diastolic
    - BP ≥ 90 mmHg or both, using the mean of three readings taken at least one
    - minute apart with the subject in a sitting position);
    - Cholestatic jaundice;
    - Known or suspected carcinoma of the breast, endometrial carcinoma or known
    - or suspected estrogen dependent neoplasia;
    - Undiagnosed abnormal genital bleeding (within 180 days);
    - Impaired liver function or disease, hepatic adenomas or carcinomas;
    - Known or suspected pregnancy; or
    - Known hypersensitivity to estrogens and/or progestins.
2. Breast feeding;
3. Chronic use of any medication that might interfere with the efficacy of OCs: Rifampin e.g., Rifadin®, Rimactane®, Rifamate®, Rifater®), barbiturates (e.g., Amytal®, Alurate®, Brevital®, Luminal®, Mebaral®, Nembutal®, Pentothal®, or Seconal®), phenylbutazone, phenytoin sodium (e.g., Dilantin®), griseofulvin (e.g., Fulvicin®, Grifulvin V®, Gris-PEG®, Grisactin®, Ultragris®), ampicillin, (e.g., Omnipen®, Principen®, Totacillin®, Unasyn®), tetracyclines (e.g., Achromycin®, Aureomycin®, Cyclopar®, Declomycin, Dynacin, Minocin, Panmycin, Retet, Sumycin, Tetrachel, Terramycin, Vectrin®, Vibramycin®, Vibra-Tabs®), St. John's Wort, or any generic equivalents
4. History of alcohol or drug abuse, which, in the opinion of the investigator, made the subject unfit for participation in the study;
5. History of an adverse experience with oral contraceptive use;

6. Use of drugs that as stated in the product labeling, required simultaneous use of contraceptives (e.g., isotretinoin [Accutane]);
7. Smoker and age ≥ 35 years at the time of the Screening Visit, or smokers who would become 35 while taking study medication;
8. History of being HIV or Hepatitis C positive;
9. History of noncompliance with any chronic medication
10. History of having received injectable hormone therapy (e.g., Depo-Provera) within the 10 months prior to screening or having a progestin-releasing intrauterine device (IUD) in place within one month prior to screening or having had a contraceptive implant removed within one month prior to screening;
11. Use of non-contraceptive hormonal therapy, administered by any route, within 3 months prior to screening;
12. Routine concomitant use of additional forms of contraception (IUD, diaphragm, spermicide, foam, contraceptive sponge, condoms) except for situations as specified in the protocol. A subject who routinely requires use of a condom for protection from STDs should be excluded;
13. Subjects who had a recent surgical or medical abortion, miscarriage, or vaginal or cesarean delivery must have had at least three consecutive spontaneous menstrual cycles or withdrawal bleeding episodes prior to screening or subjects using an extended cycle regimen must have completed at least one extended cycle of therapy including at least one withdrawal bleeding episode;
14. Hyperlipidemia (fasting cholesterol level greater than 260 mg/dl; fasting triglyceride level greater than 300 mg/dl);
15. Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam, or any laboratory finding that contraindicates the use of oral contraceptives, would confound interpretation of study results, or put the subject at risk;
16. Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap smear. Any other abnormal finding on the Pap smear that the Investigator considered clinically significant (such as "atypical squamous cells cannot exclude HSIL" [ASC-H], "atypical glandular cells" [AGC]; or any Pap result that would necessitate further evaluation by biopsy and/or colposcopy). Any screening Pap with "atypical squamous cells of undetermined significance (ASC-US) with "reflex" HPV testing done on the Pap sample. If the HPV testing was negative for high-risk types, the subject could have been enrolled; if the HPV testing is positive for high-risk types, the subject was not eligible for enrollment. Investigator's decision must be documented;
17. Had participated in any clinical investigation utilizing investigational drugs or medical devices within 30 days prior to screening or
18. Had donated or sustained a loss of more than 500 mL of blood within 30 days prior to screening.

Medical Reviewer's Comments

- *The exclusion criteria are similar to those found in other OC studies and are acceptable.*
- *Subjects were not excluded from study participation on the basis of body weight or body mass index.*

Removal of Subjects from The Study

Subjects were to be discontinued from the study in the event of any of the following:

- Any condition that, in the opinion of the investigator, contraindicated the use of OCs
- Subject requested withdrawal from the study
- Pregnancy
- Any adverse event that made continuation in the study impossible or inadvisable
- Subject was lost to follow-up
- Subject was discovered after enrollment not to have met, or to no longer meet, the protocol entrance criteria
- Subject was non-compliant with required study procedures including routine study visits and telephone follow-up
- Subject was noncompliant with diary completion and/or study medication use
- Subject required chronic therapy with medications known to interact with oral contraceptives

Subjects were considered lost to follow-up if study personnel were unable to acquire end of study information on the subject via end of study visit, telephone contact or registered letter with documented delivery.

Treatment Administered

Following the Screening Period all subjects were assigned to open label treatment with Lo Seasonique. Each subject was instructed to take, by mouth, one tablet daily at approximately the same time each day for four 91-day cycles. All subjects were planned to be "Sunday starters" and were to remain "Sunday starters" throughout the duration of the study.

Duramed Research, Inc. supplied all study drugs. The active LNG/EE combination tablet used on days 1-84 of the Lo Seasonique regimen is the same dosage strength currently used in the currently marketed "low-dose" OCs such as Alesse or Levlite. Lo Seasonique incorporates the same EE 10 mcg monotherapy formulation as the currently approved extended cycle regimen OC, Seasonique.

Following the Screening Period, all enrolled eligible subjects received Lo Seasonique. Each subject was instructed to take one tablet daily at approximately the same time each day. All subjects were planned to be "Sunday starters" and were to remain "Sunday starters" throughout the duration of the study.

The following was the process for initiating study medication:

- Fresh Starts (no prior history of OC use), Prior Users (history of OC use but not within six months prior to enrollment) or Continuous Users (history of OC use within six months prior to enrollment) who were not currently using a hormonal contraceptive, initiated study medication on the first Sunday following the first day of their next menstrual period (next spontaneous cycle following the Enrollment Visit). If this menstrual period began on a Sunday, study drug should be initiated that day.

- Continuous Users who were currently Sunday Starters completed their current cycle of therapy, including any placebo tablets (OC) or hormone free interval (patch or ring), and were to initiate study drug on the Sunday they would normally have begun their next cycle of treatment.
- Continuous Users who were not currently Sunday Starters began study medication on the first Sunday following the last day of active hormone administration of their prior contraceptive regimen. The interval between their last active hormonal administration and initiation of study medication was not to exceed 7 days (OC, patch or ring).

With the exception of Continuous Users, all subjects were instructed to use another nonhormonal method of contraception (such as condom, diaphragm, or spermicidal agent) as a back-up birth control method during the first week of drug therapy.

The following instructions were given to the subjects regarding missed pills:

- If 1 pill was missed during Weeks 1 through 12, take the pill as remembered. Take the next pill at the regular time. A back-up method of contraception was not advised except as otherwise required during week 1 of cycle 1.
- If 2 pills in a row were missed during Weeks 1 through 12, take the 2 pills on the day you remember and 2 pills the next day, then take 1 pill a day until the pack is finished. Use another non-hormonal birth control method as a back up for those 7 days if sexually active during this time period.
- If 3 pills in a row were missed during Weeks 1 through 12, resume taking 1 pill every day and contact the study site.

The use of emergency contraceptive pills was prohibited in the study.

Treatment Compliance

During treatment with study medication, subjects were allowed one lapse of up to 24 hours in pill taking per 4-week treatment period. Any additional lapse in study medication use may have resulted in withdrawal from the study at the discretion of the investigator and/or sponsor. Compliance with study medication use was assessed by a combination of the daily or weekly self-reporting by the subject in a paper diary and the pill count from the returned used pill packs that were recorded on the drug accountability case report form (CRF). Subjects were to be instructed to bring their pill pack(s) with them to each study visit and to return the study medication at the Final Study (or early termination) Visit. Treatment compliance was largely evaluated based on subjects completing their paper diaries.

Medical Reviewer's Comment

- *A total of 81 out of the 2185 (3.7%) patients who received at least one dose of study medication were discontinued from the trial due to non-compliance with the protocol.*

Subject Diaries

During the study, all subjects were to complete a paper diary to record their daily study medication use, incidence of bleeding and/or spotting and any additional forms of contraception

used. A running log was used to collect any concomitant medications taken and health related events occurring during the interval between study visits.

In order to be considered compliant with diary completion, a subject needed to complete, overall, at least 80% of the diaries. A complete diary was defined as having at least 50% of the required information based on the total number of data points expected versus entered. The subject must also have made at least one valid entry of each type of data required by the diary.

The study started with subjects using a weekly paper diary but later changed to a daily paper diary. Subjects who started with a weekly diary were instructed to continue recording on the weekly diary but all new subjects were given a daily diary. The only difference between the weekly diary and the daily diary was the question related to bleeding and spotting.

In the eight page weekly diary, subjects were asked 5 questions. These were:

1. Check the days you took your pill.
2. For the past 7 days, how many days of bleeding (defined as requiring the use of pads and/or tampons) and/or spotting do you have?
3. How many days were spotting only (defined as not requiring the use of pads and/or tampons)?
4. Did you use a condom during the past week?
5. Have you used any other form of contraception other than condoms during the past week? If yes, record the form of contraception.

The nine page daily diary asked the same questions regarding missed pills and back-up contraception. However, the daily diary was more specific with regards to bleeding and spotting. In the daily diary, subjects were asked to record bleeding or spotting for each day of the week on the scale of 0 (none), 1 (spotting), 2 (light), 3 (moderate), 4 (heavy) where spotting = <1 pads/day, light = 1-2 pads/day, moderate = 3-5 pads/day, heavy = 6+ pads/day.

Medical Reviewer's Comments

- *It's not clear in the submission why the Applicant elected to go from weekly to daily diaries.*
- *A total of 996 subjects used a weekly diary during the study and 848 subjects used a daily diary during the study.*

Study Procedures

The trial included a screening period of approximately four weeks, four consecutive 91-day cycles, and a follow-up period of approximately four weeks.

All subjects were evaluated for eligibility during the screening period. Those who met all of the inclusion criteria and none of the exclusion criteria were eligible to enroll. Following the start of study medication, subjects were to be monitored via study visits during weeks 13, 26, and 39, and by telephone approximately monthly between routine visits. All subjects, including those who completed the study and those who were withdrawn or terminated the study early, were to undergo a final study visit approximately two weeks (acceptable window was 14-21 days)

following the subject's final dose of study medication. The final study contact was to occur as a telephone call at 30 days (acceptable window was 30-45 days) following the last dose of study medication.

Study Visits

Visit 0 (Screening Visit)

The Screening Visit took place within four weeks prior to initiation of study therapy and, after obtaining informed consent, included a medical and contraceptive history, physical examination (including pelvic exam and Pap smear), vital signs (including weight), and clinical laboratory tests. Clinical laboratory tests included a CBC, serum chemistries (glucose, sodium, BUN, potassium, serum creatinine, chloride, total bilirubin, bicarbonate, alkaline phosphate, ALT, AST, albumin, total protein, inorganic phosphorus, calcium, uric acid), a lipid profile, urinalysis, and a urine pregnancy test. Subjects with a positive pregnancy test were disqualified from participation. Subjects with an abnormal pap smear were disqualified unless the investigator determined the results were not clinically significant and would not interfere with the conduct of the study.

Visit 1 (Enrollment)

At Visit 1, the first dose of study medication was given. All subjects initiated study medication on the first Sunday following the beginning of their menstrual period and were to remain as Sunday starters throughout the study.

Subjects were given urine pregnancy test kits at the Enrollment Visit to use if menses did not start as anticipated, or any time they suspected they might be pregnant. They were instructed to contact the study staff immediately in the event of a positive pregnancy test. A urine pregnancy test was to be done at all study visits and by the subject (using home urine pregnancy kits supplied to the clinical site by the Applicant) between study visits. Subjects were to report results of home urine pregnancy tests as part of phone follow up.

Visits 2, 3, and 4

These visits were to occur during Weeks 13, 26 and 39 following the first dose of study medication.

Visit 5 (Final Visit)

The Final Study Visit was to occur approximately 14 days (acceptable window was 14-21 days) following the last dose of study medication.

Telephone Follow-Up Throughout the Study

Subjects were contacted by telephone within 3 days of the anticipated study medication start date to confirm onset of the subject's menses and to confirm commencement of study medication and diary completion. Subjects were also contacted by telephone monthly between scheduled study visits to confirm negative urine pregnancy test, inquire regarding adverse events, change in smoking habits, concomitant medication use, and compliance with study mediation and diary completion.

Post Study Follow-Up

The final study contact was to be via telephone at 30 days (acceptable window was 30-45 days) following the last dose of study medication.

All subjects, including those who were withdrawn and those who discontinued the study early, were followed for the occurrence of SAEs for 30 days following the last dose of study medication. Those subjects who had an ongoing SAE that was not resolved by 30 days following the last dose of study medication were followed until the event resolved or until it was deemed chronic or stable by the Investigator.

Any subject who became pregnant during the course of the study, and who had taken at least one dose of study medication, was to be followed for eight weeks following delivery or termination of the pregnancy for safety purposes only. The infant's health was to be evaluated at birth and again at eight weeks.

The study schedule of procedures is illustrated in Table 3.

Table 3 Study Schedule By Visit

Parameter	Visit 0 Screening	Visit 1 Enrollment	Visits 2-4	Phone Follow-Up[3]	Visit 5: Completion of Therapy	Post Study Follow-Up[4]
Weeks from First dose of Study Medication	-4	0	13, 26, 39		52+2 weeks	52+4 weeks
Informed consent	X					
Medical and contraceptive history	X				X	
Physical exam including pelvic exam	X				X	
Weight, vital signs	X	X	X		X	
Pap smear	X[1]				X	
Randomization		X				
Clinical laboratory tests	X				X	
Urine pregnancy test[5]	X	X	X	X	X	X
Urine pregnancy test kits distribution		X	X		X	
Study drug distribution		X[2]	X			
Diary distribution		X	X			
Study drug compliance			X	X	X	
Diary review/collection			X		X	
Diary completion compliance			X	X		
Adverse event recording		X	X	X	X	X
Concomitant medications recording	X	X	X	X	X	X
Change in smoking habits		X	X	X	X	
Collection of study supplies					X	

[1] Subjects who had a normal Pap smear within six months prior to the Screening Visit were not required to have the test repeated if a copy of the Pap results was provided to the Investigator prior to enrollment.
[2] First dose of study medication began Week 1/Day 1.
[3] Subjects were to be contacted by telephone within 3 days of the anticipated study medication start date to confirm onset of the subject's menses (Fresh Starts, Prior Users and Continuous Users who were not on hormonal treatment at study entry) and commencement of study medication and diary completion; subjects were also to be contacted by telephone approximately monthly between scheduled study visits to confirm negative urine pregnancy test, query the subject regarding adverse events, change in smoking habits, concomitant medication use, and compliance with study medication and diary completion.
[4] The final study contact was to be via telephone at 30 days (acceptable window was 30-45 days) following the last dose of study medication.
[5] A urine pregnancy test was to be done at all study visits and by the subject (using home urine pregnancy kits supplied to the clinical site by the Sponsor) prior to the scheduled monthly phone call. Between study visits; subjects were given pregnancy test kits at the Enrollment Visit to use as needed if menses did not start as anticipated, or any time they suspected they might be pregnant; subjects were instructed to contact the study staff immediately in the event of a positive pregnancy test.

6.1.4 Efficacy Findings

Primary Efficacy Assessments

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index, using all "on-drug" pregnancies, defined as those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than 14 days after the date of the last dose of combination (LNG/EE) oral contraceptive therapy, which is generally taken on Day 84 of the cycle.

Pregnancy (on- or off-drug) was determined as follows:

- Pregnancy was defined as a positive pregnancy test verified by the study staff.
- The conception date was based on the ultrasound information when available.
- If conception clearly occurred before the date of first dose of study medication, then the pregnancy was not counted as an "on drug" pregnancy.
- If conception clearly occurred more than 14 days after the date of last combination dose of study medication, then the pregnancy was considered "off-drug" and not counted as an "on-drug" pregnancy.
- If it was unclear exactly when the conception occurred, then it was counted as an "on-drug" pregnancy.
- If no ultrasound-based estimate of conception date was available or the pregnancy status of a woman was unknown (e.g., the delivery date was unknown because the subject was lost to follow-up), then the pregnancy was counted as an "on-drug" pregnancy.
- Any reported pregnancy that could not be verified using the methods already described was defined as an "unverified pregnancy" and not counted as either an "on-drug" or "off-drug" pregnancy.

Medical Reviewer's Comments

- *The criteria for an "on-drug" pregnancy are acceptable to the Division. However, each "unverified pregnancy" was reviewed to determine if there were enough evidence to conclude that an on-drug conception occurred. The Division did not always agree with the Applicant's determination (see Table 8 Pregnancy Listings).*
- *Methods of analyzing the pregnancy rate using the Pearl Index or Life Table Analysis are described in Section 6.1.2 under General Discussion of Endpoints.*

The following cohorts were the efficacy sets analyzed by the Applicant:

Pregnancy Intent to Treat Cohorts

The principal cohort studied regarding the prevention of pregnancy included subjects between the ages of 18 and 35 years with at least one complete cycle on treatment (PITT). A "complete cycle" was defined as one where the subject completed 84 days of combination tablets. A cycle in which a subject became pregnant was considered a complete cycle, regardless of whether the

subject completed the requisite number of days of combination tablets for all pregnancy calculations.

The denominators of the Pearl Index calculations presented in the efficacy analysis by the Applicant are as follows:

- PITT excluding all cycles where another form of birth control was used: All complete cycles for subjects in the PITT cohort, excluding all 28-day cycles in which another form of birth control was used. The number of cycles from this calculation was used in calculating the primary efficacy endpoint.
- The "Typical-Use" Pregnancy Rate: All complete cycles for subjects in the PITT cohort in which no other birth control method (excluding condoms) was used.
- The "Compliant-Use" Pregnancy Rate: All complete cycles for subjects in the PITT cohort in which no other birth control method was used (excluding condoms) and the subject was deemed to be compliant during the cycle. Non-compliance was defined as all cycles in which a subject skipped two or more consecutive pills or had a pattern of substantial non-compliance (an overall compliance of less than 80%) with study medication, or used a prohibited concomitant medication that may interact with oral contraceptive therapy. Non-compliant cycles were eliminated from the PI calculation.
- The "All Users" Pregnancy Rate: All complete cycles for subjects in the PITT cohort with no excluded cycles where another form of contraception was used.
- Subsets of the cohorts listed above for subjects with body weight < 90 kg and > 90 kg.

Those cycles in which drugs known to interact with oral contraceptive therapy were taken (see Section 6.1.3 under Exclusion Criteria) were not used in the calculation of the pregnancy rate. However, pregnancies that were conceived during cycles in which such drugs (i.e., antibiotics) were used were included in the Pearl Rate calculations. Data from any subject who utilized contraceptive pills other than those provided for in the study were not included in the Pearl Rate calculations.

Pregnancy Testing

Subjects were given pregnancy test kits at the Enrollment Visit to use if menses did not start as anticipated, or any time they suspected they might be pregnant. In the event of a positive pregnancy test,. subjects were instructed to contact the study staff immediately.

In addition to the urine pregnancy test done at all study visits, subjects (using home urine pregnancy kits supplied to the clinical site by the Applicant) also performed home urine pregnancy tests prior to each telephone follow up and were instructed to report results of these tests as part of the telephone follow-up.

Table 4 lists the total reported pregnancies which occurred in Study DR-PSE-309.

Table 4 Total Reported Pregnancies (N=58)

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
5/514	26 5' 9" 172 lbs. 25	F	9/25/05	9/23/06	(b) (6)	(b) (6) by ultrasound	Off (24 days PCD***)	Off	Compliant (Premature Labor)
5/596	28 5' 10" 198 lbs. 28	F	1/22/06	7/25/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
6/628	24 5' 7" 119 lbs. 19	C	10/9/05	3/5/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
6/680	23 5' 8" 188 lbs. 29	P	3/19/06	5/13/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
8/801	24 5' 8" 208 lbs. 32	P	9/11/05	4/11/06	(b) (6)	Patient reported ectopic by ultrasound of (b) (6)	Off (Patient reported but unverified pregnancy)	On	Compliant
8/812	23 5' 5" 184 lbs. 31	P	10/9/05	10/2/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
10/1014	35 5' 2" 122 lbs. 22	P	7/31/05	7/29/06	(b) (6)	(b) (6) by ultrasound	On (11 days PCD)	On	Non-Compliant; never used post-study OCs
10/1096	23 5' 1" 110 lbs. 21	P	11/14/05	Unknown	Unknown	(b) (6) (Imputed per patient report)	Off (Patient reported pregnancy but unverified)	On	Non-Compliant; lost to f/u, missed 4-5 combination pills
10/10168	26 5' 2" 179 lbs. 33	P	2/26/06	7/26/06	(b) (6)	(b) (6) (Imputed)	On (Miscarriage)	On	Compliant
13/1333	36 5' 8" 163 lbs. 25	C	10/2/05	5/20/06	(b) (6)	(b) (6) by ultrasound	Off (16 days PCD)	Off	Compliant

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
13/1345	21 5' 3" 126 lbs. 22	F	11/27/05	11/18/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
13/1355	23 5' 1" 165 lbs. 31	F	Drug dispensed 12/14/05 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
13/1359	28 5' 3" 117 lbs. 21	C	2/5/06	6/17/06	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two or more pills
13/1362	22 5' 7" 233 lbs. 37	F	2/12/06	1/6/07	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
14/1433	21 5' 7" 170 lbs. 27	C	9/18/05	12/10/05	(b) (6)	(b) (6) by ultrasound	Off (22 days PCD)	Off	Unknown
15/1515	18 5' 2" 130 lbs. 24	C	8/14/05	12/5/05	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two pills
16/1633	24 5' 2" 147 lbs. 27	P	9/11/05	12/14/05	(b) (6)	(b) (6) by ultrasound	Off (43 days PCD)	Off	Compliant
17/1703	21 5' 4" 130 lbs. 22	P	9/4/05	3/31/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
18/1869	21 5' 6" 221 lbs. 36	P	4/9/06	7/6/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
19/1932	35 5' 2" 204 lbs. 37	C	12/4/05	12/31/05	(b) (6)	(b) (6) by ultrasound	Off	Off	Conceived during screening
19/1954	26 5' 8" 212 lbs. 32	P	Drug dispensed 1/23/06 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
19/1971	20 5' 2 " 266 lbs 49	P	4/2/06	4/9/06	(b) (6) 6	(b) (6) by ultrasound	Off	Off	Conceived during screening

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
21/2112	27 5' 7" 166 lbs. 26	C	10/30/05	5/24/06	(b) (6)	(b) (6) by ultrasound	Off (21 days PCD)	Off	Unknown
23/2337	25 5' 5" 141 lbs. 23	P	Drug dispensed 11/10/05 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
24/2421	24 5' 1" 117 lbs. 22	P	8/21/05	4/22/06	(b) (6) (ßHCG=697)	(b) (6) by ultrasound	Off (26 days PCD)	Off	Compliant
25/2504	22 5' 3" 296 lbs. 50	P	Drug dispensed 8/3/05 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
25/2571	22 5' 5" 140 lbs. 23	C	12/4/05	2/18/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
25/2599	24 5' 4" 133 lbs. 23	P	2/26/06	5/27/06	(b) (6) (ßHCG=2866)	(b) (6) by ultrasound	Off (Miscarriage)	Off	Compliant
25/25110	35 5' 7" 198 lbs. 31	P	Drug dispensed 2/24/06 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
29/2905	23 5' 4" 144 lbs. 25	C	8/14/05	10/21/05	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two pills
29/2909	33 5' 7" 283 lbs. 44	C	9/18/05	4/16/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant (Twins)
29/2910	35 5' 9" 157 lbs. 23	F	Drug dispensed 7/14/05 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening
35/3562	26 5' 3" 143 lbs. 25	P	3/26/06	3/24/07	(b) (6)	(b) (6)	On	On	Non-Compliant; skipped two or more pills
36/3611	24 5' 2" 151 lbs. 28	P	Drug dispensed 10/14/05 but never started		(b) (6)	Unknown	Off	Off	Conceived during screening

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
37/37104	27 5' 4" 150 lbs. 26	C	3/19/06	5/15/06	(b) (6)	Patient reported abortion on (b) (6)	Off (Patient reported but unverified pregnancy)	On	Compliant; lost to f/u after 5/15/06
37/37110	26 5' 7" 247 lbs. 39	C	4/9/06	7/11/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
37/37111	18 5' 4" 142 lbs. 24	C	4/16/06	10/12/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
42/4212	27 5' 7" 211 lbs. 33	P	9/25/05	9/23/06	(b) (6)	(b) (6) by ultrasound	Off (21 days PCD**)	Off	Compliant
44/4415	27 5' 4" 112 lbs. 19	C	7/17/05	7/15/06	(b) (6)	(b) (6) by ultrasound	Off (21 days PCD**)	Off	Compliant
44/4457	27 5' 8" 249 lbs. 37	C	10/9/05	10/7/06	(b) (6)	(b) (6) by ultrasound	Off (18 days PCD**)	Off	Compliant
44/4486	24 5' 3" 107 lbs. 19	C	Drug dispensed 2/10/06 but never started		(b) (6) (ectopic)	Unknown	Off	Off	Conceived during screening
44/4489	23 5' 8" 147 lbs. 22	C	2/26/06	11/20/06	(b) (6)	Missed abortion	On	On	Compliant
45/4501	25 5' 0" 108 lbs. 108 21	C	11/6/05	10/28/06	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; took amoxicillin 9/8/06 to 9/15/06 without back-up
46/4604	29 5' 0" 187 lbs. 37	P	10/30/05	8/1/06	(b) (6) (ßHCG=194)	(b) (6) by ultrasound	On	On	Compliant

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
47/4714	19 5' 9" 270 lbs. 40	F	8/14/05	Unsure (7/16/06 or 8/14/06)	(b) (6)	(b) (6) based on LMP	On	On	Non-Compliant; skipped two or more pills
50/5004	21 5' 3" 127 lbs. 22	P	3/12/06	9/11/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
50/5006	25 5' 10" 175 lbs. 25	C	2/26/06	3/22/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
53/5307	31 5' 1" 168 lbs. 32	P	8/14/05	11/8/05	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
53/5317	24 5' 3" 215 lbs. 38	P	Drug dispensed 7/29/05 but never started		(b) (6)	Unknown by ultrasound	Off	Off	Conceived during screening
53/5341	28 5' 3" 172 lbs. 30	P	11/20/05	11/3/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
54/5433	22 5' 6" 169 lbs. 27	P	2/19/06	2/1/07	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped 2 pills in cycle 4
56/5618	23 5' 0" 131 lbs. 26	P	8/14/05	8/12/06 (Last PCD 8/5)	(b) (6) (ßHCG=10,133)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two pills
56/5639	27 5' 7" 142 lbs. 22	C	10/23/05	9/14/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant
56/5660	32 5' 6" 140 lbs. 23	P	2/5/06	10/24/06	(b) (6)	(b) (6) by ultrasound	On (Miscarriage)	On	Compliant
58/5803	34 5' 4" 174 lbs. 30	P	7/31/05	7/31/05	(b) (6)	(b) (6) by ultrasound	Off	Off	Took only one pill; conceived during screening

Site # Pt #	Age(yrs) Height Weight BMI	User Type	Drug Start Date	Drug Stop Date*	Date of Positive Pregnancy Test	Conception Date	Applicant Considers Conception On/Off Drug**	MO Considers Conception On/Off Drug**	MO Evaluation of Compliance
59/5918	24 5' 1" 145 lbs. 27	P	10/9/05	3/5/06	Unknown	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two pills
59/5925	33 5' 3" 161 lbs. 29	P	11/20/05	5/17/06	(b) (6)	(b) (6) by ultrasound	On	On	Non-Compliant; skipped two pills
59/5947	27 5' 4" 154 lbs. 26	P	3/5/06	10/21/06	(b) (6)	(b) (6) by ultrasound	On	On	Compliant

* Drug Stop Date does may include date subject completed EE-alone tablets
** "On drug" is defined as conception occurring from first dose of study drug to 14 days post last combination dose
*** "PCD" = post combination dose
C: Continuous Users (History of OC use for an interval of at least three successive cycles with regular withdrawal bleeding prior to enrollment)
P: Prior Users (No history of OC use in the six months prior to enrollment)
F: Fresh Starts (No prior history of OC use)
Source: NDA 222-262, Clinical Study Report, Adapted from the Narrative Summaries and Case Report Forms

Medical Reviewer's Comments

- *Nine subjects (Subjects 1355, 1954, 2337, 2504, 25110, 2910, 3611, 4486, and 5317) became pregnant during the screening phase of this study prior to taking study medication.*
- *Subject 58/5803 conceived during screening but was enrolled in the study. She took only one tablet of study drug prior to having a positive pregnancy test.*
- *Subject 19/1971 conceived during screening but was enrolled in the study. She only took eight days of study medication.*
- *The Applicant originally determined that there were a total of 33 on-drug pregnancies during this trial. When the case report forms were reviewed, the Medical Reviewer believed that three additional conceptions probably occurred "on drug," resulting in a total of 36 "on-drug" pregnancies.*
- *A total of 12 of the 36 on-drug pregnancies occurred in subjects who were non-compliant.*
- *Based on the total of 36 on-drug pregnancies, the Pearl Index for Lo Seasonique, as calculated by the FDA Statistician, is* ***2.74 (95% CI: 1.92, 3.78)****.*
- *An electronic submission from the Applicant dated 6/20/08 disagreed with the Division's opinion that subjects 8/801, 10/1096, and 37/37104 conceived "on-drug." The Applicant believes that "on-drug" pregnancies must be verified or documented by "hard" evidence such as a positive pregnancy test obtained at the study site. They also believe that there must be some reasonable evidence presented of reliable pill taking, such as returned subject diaries or drug accountability information. The Division believes that the case report forms for subjects 8/801, 10/1096, and 37/37104 provide sufficient evidence that an on-drug pregnancy may have occurred with these subjects.*
    - *Patient 8/801 discontinued study drug on 4/11/2006 after having a positive pregnancy test. She was diagnosed as having an ectopic pregnancy on ultrasound and subsequently had laparoscopic surgery performed on* (b) (6) *In a phone conversation with the patient documented in the case report form (Pregnancy Notification Form), she stated that she was compliant with taking the study drug. The Applicant believes that since there were no returned pill packs or diary, the pregnancy should be considered off-drug.*
    - *Patient 10/1096 called the study site on 3/27/06 and told a coordinator that she was 3-4 weeks pregnant and had missed 4-5 active pills during the month of February. The patient was non-compliant and was lost to follow-up, but this reviewer believes she conceived while taking study drug. The Applicant believes that since there was no objective verification by diary or drug accountability, the pregnancy occurred off-drug.*
    - *Patient 37/37104 began study drug on 3/19/06 and had a positive pregnancy test on 5/15/06. On 6/19/06, she informed the study site that she had a medical abortion. The patient never returned after her initial study visit and her date of*

conception was unknown. The Applicant believes that the lack of objective data fail to support that she even started the pills.

Primary Efficacy Endpoints

The efficacy calculation is based on completed cycles in the 18-35 year age range (PITT cohort) and excludes cycles where other birth control methods were utilized.

Table 5 Pearl Index Calculations Using 28-Day Cycle Intervals

	N	Total Number of 28-Day Completed Cycles	Cycles With Other Birth Control	Cycles Without Other Birth Control	Number of "On-Drug" Pregnancies	Pearl Index Based on Cycles without other Birth Control	95% Confidence Interval
Applicant	1,728	17,974	909	17,065	33	2.51	(1.73, 3.53)
Medical Reviewer	1,729	17,977	909	17,068	36	2.74	(1.92, 3.78)

Source: NDA 21-262, CSR, Page 524, Table 95 and Page 527, Table 103; Medical Reviewer's calculation of "on-drug" pregnancies, and FDA Statistician's review.

Table 6 Pearl Index Calculations Using 91-Day Cycle Intervals

	N	Total Number of 91-Day Completed Cycles	Cycles With Other Birth Control	Cycles Without Other Birth Control	Number of "On-Drug" Pregnancies	Pearl Index Based on Cycles without other Birth Control	95% Confidence Interval
Applicant	1,649	5,461	572	4,889	33	2.70	(1.86, 3.79)
Medical Reviewer	1,650	5,464	572	4,892	36	2.94	(2.07, 4.06)

Source: NDA 21-262, CSR, Page 71; Medical Reviewer's calculation of "on-drug" pregnancies, and FDA Statistician's review.

Medical Reviewer's Comments

- *Based on 36 on-drug pregnancies occurring over 17,068 completed 28-day cycles, where no other birth control method was used, the Pearl Index for Lo Seasonique was calculated by the FDA Statistician to be 2.74 (95% CI: 1.92, 3.78). This is the primary analysis used by the Division, and should be reported in labeling.*
- *Based on 36 on-drug pregnancies occurring over 4,892 completed 91-day cycles, where no other birth control method was used, the Pearl Index for Lo Seasonique was calculated by the FDA Statistician to be 2.94 (95% CI: 2.0, 4.06). The higher Pearl Index is due to the exclusion of 91-day cycles in the latter analysis, even if another method of birth control were used only once in the 91-day period. In the 28-day cycle analysis, only 28-day cycles in which other birth control methods were used were excluded, thus the number of cycles at risk is higher.*
- *Pearl Indices for other approved extended cycle OCs include:*
  - *Seasonale (NDA 21-544): 1.97 (95% CI: 0.54, 5.03)*
  - *Seasonique (NDA 21-840): 1.77 (95% CI: 0.7, 3.64)*
  - *Lybrel (NDA 21-864): 2.39 (95% CI: 1.57, 3.62)*

Life Table Calculations

According to the FDA Statistician, the life table pregnancy rate in treated subjects 18-35 years of age using all completed 91-day cycles and 36 pregnancies is 3.2% (95% CI: 1.2, 5.2).

Medical Reviewer's Comment

- *The life table cumulative one year pregnancy rate of 3.2% includes all subjects between the ages of 18 and 35 who completed at least one 91-day cycle of treatment. Unlike the Pearl Index calculations, this method requires an uninterrupted time interval of participation, therefore, no cycles are excluded from this calculation.*

Body Mass Index and Pregnancy Rates

There is a concern that contraceptive efficacy may be impaired with low dose oral and transdermal combination contraceptives, particularly in heavier women. Therefore, the FDA Statistician was asked to analyze the occurrence of on-drug pregnancies by weight deciles (See Table 7).

Table 7 On-Drug Pregnancies and Weights, PITT Cohort

Weight (lbs.)	On-Drug Pregnancies (N=36)
87 – 116	2
117 – 125	3
126 – 133	5
134 – 140	2
141 – 148	6
149 – 157	2
158 – 170	3
171 – 187	5
188 – 217	3
218 – 391	5

Source: Based on calculations made by Sonia Castillo, Ph.D., from data provided by the Applicant on June 3, 2008

The Statistician determined that there were no obvious relationships between drug failure and patient weight.

Medical Reviewer's Comments

- *The proportion of Americans who are obese (body mass index > 30) has increased. Effects of high body weight on drug absorption are not completely understood; however, an increased volume of distribution, as occurs in heavier women, may decrease serum contraceptive steroid levels.*
- *Although the numbers are small, no trend was detected regarding decreased contraceptive efficacy with increased subject weight. Half of the on-treatment pregnancies occurred in the lower five deciles of weight, and half in the upper five deciles.*

6.1.5 Clinical Microbiology

The original application did not contain the discussion of microbiological properties. Duramed justified the absence of microbial testing of the drug product in the amendment dated 6/6/2008. The Applicant stated that the microbiological safety of the drug product is assured because water level is controlled at multiple stages of the drug production to prevent microbial growth. In addition, both Seasonale and Seasonique were approved without microbial limit tests.

Medical Reviewer's Comment

- *The FDA chemist, in his review, stated that the Applicant's justification presented above is adequate and warrants the absence of microbial testing.*

6.1.6 Efficacy Conclusions

Efficacy is based on Lo Seasonique's ability to prevent pregnancy in a single phase 3 clinical trial (DR-PSE-309). In this trial, Lo Seasonique was given for one year to women ages 18-35 desiring pregnancy prevention. The most conservative approach to calculate the Pearl Index was employed. Only women ages 18-35 were used for the calculation. All incomplete cycles (less than 28 days) and cycles where additional birth control methods were used (including condoms), other than those in which a pregnancy occurred, were also excluded from the PI calculation.

The results of Study PSE-DR-309 provide evidence that Lo Seasonique when taken for one year is effective in preventing pregnancy in women desiring oral contraception. The efficacy was demonstrated by a Pearl Index of 2.74, which is consistent with low-dose OC products. Subjects also demonstrated pill compliance and study discontinuation rates which were consistent with what has been observed in other low dose OC studies. The 17,068 28-day cycles is considered sufficient exposure to determine oral contraceptive efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was evaluated by assessment of adverse events, concomitant medications, clinical laboratory evaluations, vital signs (including weight), physical examinations, and the frequency of bleeding and/or spotting. Clinical and laboratory adverse events (AEs) reported during the treatment phase of the study served as the principal means to evaluate safety.

The Safety Cohort studied consisted of 2,185 subjects who received at least one dose of study drug, whether or not the subjects ever returned for any post-baseline study visit. Subjects for whom dose verification could not be established were included, with the assumption that they took at least one dose of study medication. This was the cohort studied for the evaluation of all safety endpoints, (i.e., adverse events, vital signs, and laboratory evaluations).

The Intent to Treat Cohort consisted of 1,950 subjects who were randomized to treatment and completed at least one extended cycle (at least 84 days of combination therapy) of study medication. The ITT cohort was the principal subject cohort for the evaluation of bleeding and/or spotting days.

Medical Reviewer's Comments

- *Combination oral contraceptive products containing LNG and EE have been marketed for decades worldwide, and in the United States since 1968 (Ovral).*
- *There is a very large safety database for both of the active components of Lo Seasonique (LNG and EE). These components are found in many approved combined oral contraceptives. A table listing the NDA application numbers, approval dates and*

dosages for combination oral contraceptives that contain both LNG and EE is found in the Appendix (Section 10). These products include Ovral, Lo-Ovral, Nordette, Triphasil, Alesse, and Levlite. In addition, LNG is used alone as a contraceptive in Norplant, Norplant II, Mirena, and Plan B.

Safety was evaluated in the following manner for Study DR-PSE-309:

- Subjects were instructed to contact their investigator for any serious side effect
- Emergency contacts were established for expeditiously handling serious adverse events (SAEs)
- Subjects were provided with paper adverse events diaries to record the event and the start/stop dates
- The paper diary additionally captured typical symptoms occurring around the time of a withdrawal period with weekly questions.
- Adverse Events (AEs) were reported during regular monthly telephone contacts and at the subject's regularly scheduled visits to the investigational site. Site personnel recorded information about AEs on the AE case report form (CRF).
- Adverse events were classified according to the MedDRA system.
- Clinical safety labs were performed at screening and completion of the study.

7.1.1 Deaths

There were no reported deaths during this study.

7.1.2 Other Serious Adverse Events

A total of 34 (1.6% of the 2185) treated subjects reported at least one SAE during the course of this study. Only two subjects were reported to have discontinued the study due to a SAE.

Subject 24/2423 was a 29 year old Caucasian smoker who was a prior user of OCs. The patient had a previous history of illicit drug use, which was not disclosed during screening. She took her first dose of study drug on September 11, 2005 and her last dose on November 9, 2005. On November 15, 2005, during a phone conversation with the study site, the patient's mother reported that the patient had also begun illicit drug use on (b) (6) She discontinued the study on (b) (6) and entered a substance abuse rehabilitation program for treatment in another state. She was not able to continue in the study. This was listed as a SAE by the Investigator under the term "illicit drug use." The Investigator did not consider it related to study medication.

Subject 44/44104 was a 22 year-old Caucasian smoker who was a prior user of OCs. The patient began taking Lo Seasonique on April 2, 2006. On May 28, 2006, she experienced frontal headaches which were similar to headaches she had experienced three years prior. On June 8, 2006, she began treating the headaches with Wellbutrin. On (b) (6) , the patient was driving with her mother to the hospital when she experienced a syncopal episode that lasted approximately 3-5 seconds, at which time her mother grabbed the steering wheel. The patient

presented to the emergency room complaining of intermittent headaches with blurred and double vision, as well as the syncopal episode she had experienced. She was diagnosed with headache (intermittent) and syncope (serious, severe, and possibly related to study medication). She was treated with intravenous Ketorolac for the headaches and was admitted to a telemetry unit for a diagnostic workup and further monitoring. An echocardiogram and CT scan were obtained and all results were normal. A qualitative serum B-HCG was performed and was negative. Her pulse oximetry was 99-100% on room air. Hematology, coagulation, and chemistry panel values were all within normal limits. D-dimer, TSH, and B-type natriuretic peptide were normal. The patient was discharged from the hospital on (b) (6) and prescribed Tylenol as needed for headaches. She was instructed to refrain from driving for two days, follow-up with her primary care physician, and obtain an electroencephalogram as an outpatient. On June 13, 2006, the patient had a site visit and was discontinued from the study. She took her last dose of study medication on the same day. At the final study visit on June 29, 2006, her laboratory results, and physical and gynecological examinations, including Pap smear, were unremarkable. The patient reported her headaches resolved on July 12, 2006.

Serious adverse events reported for Lo Seasonique are listed in Table 8 by subject. Also listed is the likely relationship of the adverse events to study drug as assessed by the investigator and whether the subject discontinued participation in the trial because of the adverse event.

Table 8 Serious Adverse Events by Study Site, Safety Cohort

Site #	Subject (N=34)	Serious Adverse Event (SAE)	Relationship to Study Drug	Subject Discontinued
0001	115	Tylenol Overdose	None	No
0002	231	Migraine	Possible	No
0005	5109	Depression with Suicidal Ideation	Remote	No
	514	Premature Labor	None	No
	519	Exacerbated Asthma	Remote	No
		Urticaria	Remote	No
	520	Cholelithiasis	Possible	No
	566	Biliary Dyskinesia	None	No
0006	650	Dilated Biliary Common Duct	Possible	No
		Right Upper Quadrant Pain	Remote	No
0008	801	Ectopic Pregnancy	None	No
0010	10168	Miscarriage	None	No
	1041	Exacerbation of Asthma	None	No
0020	2010	Cholecystitis	Possible	No
0024	2423	Illicit Drug Use	None	Yes
0025	2599	Miscarriage	None	No
0026	2613	Leukocytosis	None	No
0031	3118	Right Tibial Fracture	None	No
0033	3306	Cleft Palate Repair	None	No
		Surgical Wound Breakdown	None	No
	3331	Gastroenteritis	Possible	No
	3346	Viral Meningitis	None	No
0035	3559	Appendicitis	None	No
0037	3724	Depression	Remote	No
0043	4312	Cervical Radiculopathy	None	No
0044	44104	Headache (Intermittent)	Possible	Yes
		Syncope	Possible	No
	4489	Missed Abortion	Remote	No
0046	4619	Appendicitis	None	No
	4628	Facial Fracture	None	No
0047	4706	Strep Throat	None	No
	4709	Broken Collarbone	None	No
0054	5438	Back Pain	None	No
0056	5618	Hypospadias of Infant	Remote	No
	5623	Pyelonephritis	None	No
	5660	Miscarriage	None	No
0059	5925	Spontaneous Abortion	None	No
	5932	Worsening Supraventricular Tachycardia	None	No

Source: NDA 22-262, CSR, Page 84-85

Medical Reviewer's Comments

- *This reviewer concurs that the serious adverse events in these studies were possibly but not necessarily related to study drug administration.*
- *No cases of deaths or venous thromboembolic events (VTEs) were reported in this study.*
- *There are no new signals of unexpected serious adverse events related to the use of Lo Seasonique.*

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Subject Disposition

Among all treated subjects (Safety Cohort), the most common reasons for discontinuation from this study were loss to follow-up (13.9%), adverse events (11.6%), and subject request to be withdrawn (10.3%). The most commonly reported adverse event leading to study discontinuation was metrorrhagia or "intermenstrual bleeding" (Section 7.1.3.3). This occurred in 70 (or 3.2% of the 2185 subjects). Any other adverse event leading to study discontinuation was observed in less than 1% of treated subjects.

Bleeding and/or spotting episodes were cited as the reason for study discontinuation both through adverse events and subject decision to withdraw. A total of 89 (4.1%) of discontinuations due to AEs were related to bleeding and/or spotting. Bleeding/spotting was cited as at least partially responsible for the subject's decision to withdraw in an additional 94 (4.3%) subjects.

Table 9 Disposition of All Treated Subjects

Protocol DR-PSE-309	ITT Cohort (N=1950)	PITT Cohort (N=1735)	Safety Cohort (N=2185)
Completed Study	1249 (64.1%)	1091 (62.9%)	1249 (57.2%)
Discontinued Study	701 (35.9%)	644 (37.1%)	936 (42.8%)
Primary Reason for Discontinuation			
Lost to Follow-Up	260 (13.3%)	244 (14.1%)	304 (13.9%)
Adverse Event	160 (8.2%)	143 (8.2%)	253 (11.6%)
Bleeding and/or Spotting Related	61 (3.1%)	53 (3.1%)	89 (4.1%)
Subject Request	165 (8.5%)	149 (8.6%)	225 (10.3%)
Bleeding and/or Spotting Related	69 (3.5%)	61 (3.5%)	94 (4.3%)
Non-Compliance with Study Protocol	62 (3.2%)	53 (3.1%)	81 (3.7%)
Pregnancy	27 (1.4%)	30 (1.7%)	36 (1.6%)
Did Not Meet Protocol Requirements	9 (0.5%)	9 (0.5%)	14 (0.6%)
Investigator's Discretion	1 (0.1%)	1 (0.1%)	3 (0.1%)
Other/Unknown	17 (0.9%)	15 (0.9%)	22 (1.0%)

Source: NDA 22-262, CSR, Tables 4, 5, and 6, Pages 55-57

Medical Reviewer's Comments

- *In the Safety Cohort, 94 of the 225 subjects (42%) in the "Subject Request" group cited bleeding and/or spotting as contributing to the decision to withdrawal.*
- *The overall discontinuation rate for Lo Seasonique in the Safety cohort of 2185 subjects was 42.8%. This percentage is similar to other extended cycle OCs. Seasonale (NDA 21-544) had an overall discontinuation rate in the Safety cohort of 40.6% and Seasonique (NDA 21-840) had a discontinuation rate in the Safety cohort of 50.3%. The discontinuation rate for the recently approved Lybrel was 56.8%.*
- *A total of 1,249 subjects fully completed treatment over one year. This exceeds the FDA recommended subject exposure which is of 200 women for ≥ 12 months in order to adequately assess safety.*

7.1.3.2 Adverse events associated with dropouts

The overall study discontinuation rate due to adverse events for Lo Seasonique was 11%. The adverse events resulting in study discontinuation are listed in Table 10.

The most commonly reported adverse event leading to study discontinuation was metrorrhagia which occurred in 70 of the 2185 treated subjects (3.2%). Menorrhagia was reported as an AE leading to study discontinuation in 19 subjects (0.9%) and vaginal hemorrhage in 16 subjects (0.7%). As noted in Section 7.1.3.1, Table 9 (Disposition of All Treated Patients) more than 8% of subjects discontinued the study due to adverse events that were considered, at least in part, to be bleeding and/or spotting related.

Table 10 Adverse Events Leading to Study Discontinuation, Safety Cohort

MedDRA System Organ Class or Preferred Term	Lo Seasonique (N=2185)	
Discontinuation Reason*	N	%
Reproductive System Disorders-Total	**117**	**5.4**
Metrorrhagia	70	3.2
Menorrhagia	19	0.9
Vaginal Hemorrhage	16	0.7
Breast Tenderness	4	0.2
Dysmenorrhea	3	0.1
Uterine Hemorrhage	1	0.1
Menstruation Irregular	1	0.1
Psychiatric Disorders-Total	**39**	**1.8**
Mood Swings	11	0.5
Depression	10	0.5
Nervous System Disorders-Total	**26**	**1.2**
Headache	15	0.7
Migraine	8	0.4
Skin and Subcutaneous Disorders-Total	**23**	**1.1**
Acne	12	0.6

MedDRA System Organ Class or Preferred Term	Lo Seasonique (N=2185)	
Alopecia	4	0.2
Pigmentation Disorder	2	0.1
Gastrointestinal Disorders-Total	**19**	**0.9**
Nausea	12	0.6
Abdominal Pain	3	0.1
Investigations-Total	**18**	**0.8**
Weight Gain	11	0.5
Blood Pressure Increased	6	0.3
Blood Triglycerides Increased	1	0.1
General Disorders-Total	**14**	**0.6**
Irritability	9	0.4
Chest Pain	2	0.1
Fatigue	2	0.1
Infections and Infestations-Total	**4**	**0.2**
Musculoskeletal and Connective Tissue Disorders-Total	**3**	**0.1**
Muscle Spasms	2	0.1
Musculoskeletal Chest Pain	1	0.1
Vascular Disorders-Total	**3**	**0.1**
Hypertension	2	0.1
Hemorrhage	1	0.1
Metabolism and Nutrition Disorders	**2**	**0.1**
Non-Insulin Dependent Diabetes	1	0.1
Hypoglycemia	1	0.1
Cardiac Disorders-Total (Tachycardia)	**1**	**0.1**
Eye Disorders-Total (Visual Disturbance)	**1**	**0.1**
Immune System Disorders (Anaphylactic Reaction)	**1**	**0.1**
Injury-Total (Traffic Accident)	**1**	**0.1**
Renal and Urinary Disorders-Total (Dysuria)	**1**	**0.1**
Respiratory-Total (Dyspnea)	**1**	**0.1**
Social Circumstances-Total (Drug Abuser)	**1**	**0.1**

*In some instances, 2 reasons for discontinuation were reported for a subject. Thus the total number of events in a treatment group may exceed the total number of subjects in that group who discontinued.
Source: NDA 22-262, CSR, Adapted from Table 145, Page 587-589

Medical Reviewer's Comments

- *A total of 253 subjects (11% of enrolled subjects) discontinued the study because of an adverse event.*
- *Approximately 6.3% of Seasonique treated subjects discontinued, at least in part, due to bleeding and/or spotting (NDA 21-840) and 6.1% of Seasonale treated subjects discontinued for the same reason (NDA 21-544).*

7.1.3.3 Other significant adverse events

The most significant adverse events in terms of incidence were the bleeding problems of menorrhagia and intermenstrual bleeding.

Cycle Control

Bleeding and/or Spotting

The study started with subjects (n = 996) using a weekly paper diary but later changed to a daily paper diary. Subjects who started with a weekly diary were instructed to continue recording on the weekly diary; however all new subjects (n = 848) were given a daily diary. In the weekly diaries, subjects were asked "For the past 7 days, how many days of bleeding and/or spotting do you have (defined as requiring the use of pads and/or tampons)?" and "How many days were spotting only (did not require the use of pads and/or tampons)?" whereas in the daily diaries, subjects were asked to record bleeding or spotting for each day of the week on the scale of 0 (none), 1 (spotting), 2 (light), 3 (moderate), 4 (heavy) where spotting = <1 pads/day, light = 1-2 pads/day, moderate = 3-5 pads/day, heavy = 6+ pads/day.

The following parameters were analyzed by the Applicant:

- Total number of bleeding days reported
- Number of "unscheduled" bleeding days reported (defined as bleeding during the 84 days of combination therapy)
- Total number of spotting days reported
- Number of "unscheduled" spotting days reported (defined as spotting during the 84 days of combination therapy)
- Number of "scheduled" bleeding and/or spotting days reported (defined as bleeding and/or spotting during the 7 day EE 10 mcg monotherapy interval on days 84-91).

Results for total, unscheduled and scheduled bleeding and/or spotting are calculated for all subjects who completed at least one complete 91-day cycle of therapy (ITT cohort).

Medical Reviewer's Comments

- *Unscheduled or unanticipated bleeding and/or spotting (often called "breakthrough" bleeding or spotting) is the most important cycle control parameter to review as this is the major concern in most patients.*
- *The frequency of unscheduled bleeding and/or spotting was generally similar across all four extended cycles regardless of whether a weekly or daily diary was used. Subjects using the daily diaries, however, did record slightly more bleeding and/or spotting days than subjects using the weekly diaries.*

Total Days of Bleeding and/or Spotting by Cycle

The total number of days of bleeding and/or spotting by cycle is presented in Table 11 for all treated subjects who completed at least one cycle of treatment (ITT cohort). The information in this table is an average of the daily and weekly diary reports from this cohort.

Table 11 Total Days of Bleeding and/or Spotting by Cycle (Summary of Daily and Weekly Diary Reports)

Cycle	N (All Subjects with at least one complete cycle)	Mean Total Bleeding/Spotting Days	Mean Total Bleeding/Spotting Days Per Subject-Month[1]	Median Total Bleeding/Spotting Days	Median Total Bleeding/Spotting Days Per Subject-Month[1]
1	1,802	22.1	6.8	18	5.5
2	1,547	14.8	4.6	10	3.1
3	1,351	12.5	3.9	8	2.5
4	1,199	11.1	3.4	7	2.2

[1]Obtained by multiplying the 91-day cycle by 28/91
Source: NDA 22-262, CSR, Adapted from Table 161, Page 637

Medical Reviewer's Comment

- *As seen in Table 11, patients who continue taking the pill will have decreased total bleeding and/or spotting over time. This could partially be due to patients with higher rates of bleeding and/or spotting discontinuing the study over time.*

Table 12 compares total bleeding days as recorded by subjects completing daily diaries versus weekly diaries.

Table 12 Total Days of Bleeding and/or Spotting by Cycle by Daily vs. Weekly Diary Reports

Cycle	All Subjects with at least one complete cycle (N)	Total Bleeding and/or Spotting Days Mean/Median	Subjects Using Daily Diaries (n)	Total Bleeding and/or Spotting Days Mean/Median	Subjects Using Weekly Diaries (n)	Total Bleeding and/or Spotting Days Mean/Median
1	1,802	22.1 / 18	848	24.6 / 20	996	19 / 14
2	1,547	14.8 / 10	728	17.1 / 13	852	12.2 / 8
3	1,351	12.5 / 8	656	14.2 / 9	726	10.5 / 7
4	1,199	11.1 / 7	574	12.8 / 9	644	9.2 / 5

Source: NDA 22-262, CSR, Adapted from Table 161, 162, and 163 Page 637

Medical Reviewer's Comments

- *As I interpret the data, the total days of bleeding and/or spotting per cycle did not differ significantly in subjects using daily or weekly diaries. The subjects completing daily diaries probably had better recall to capture slightly more total bleeding/spotting days.*
- *The unscheduled and scheduled bleeding and/or spotting tables below will combine both weekly and daily diary data.*

Unscheduled Bleeding and/or Spotting by Cycle and Subject Month

The total number of days of unscheduled bleeding and/or spotting by cycle is presented in Table 12 for all treated subjects in the ITT cohort. The information presented in this table is a summary of the daily and weekly diary reports from this cohort.

Table 13 Unscheduled Bleeding and/or Spotting Days per 91-Day Cycle and per Patient-Month, ITT Cohort

Lo Seasonique Cycle	N	Mean Days	Mean Per Subject-Month[1]	Median Days	Median Per Subject-Month[1]	Minimum/Maximum Days
1	1,802	19.6	4.9	15	3.8	0 / 84
2	1,547	12.4	3.1	8	2.0	0 / 84
3	1,351	10.3	2.6	6	1.5	0 / 83
4	1,199	8.6	2.2	5	1.3	0 / 66

[1]Obtained by multiplying the 91-day cycle by 21/84
Source: NDA 22-262, CSR, Adapted from Table 164, Page 639

Medical Reviewer's Comments

- *Unscheduled bleeding and spotting are both undesirable from a patient's viewpoint.*
- *As shown above in Table 13, unscheduled bleeding and/or spotting decreases by the 4th cycle of therapy.*
- *Although total and unscheduled bleeding and/or spotting can be problematic with extended cycle oral contraceptives, baseline and end of treatment hemoglobin and hematocrit values for subjects taking Lo Seasonique do not raise any safety concerns.*

The analysis of unscheduled and/or spotting data was based on subjects with completed cycles only (ITT Cohort). The Division requested the Applicant to recalculate the unscheduled and/or spotting data based on all subjects who received at least one dose of study medication (Safety Cohort). This data was generated by the Applicant and submitted to the Division on September 5, 2008. Table 14 is based on combined weekly and daily diary data.

Table 14 Unscheduled Bleeding and/or Spotting Days per 91-Day Cycle and per Patient-Month, Safety Cohort

Lo Seasonique Cycle	N	Mean Days	Minimum Days	Median Days	Maximum Days	Median Days Per Patient -month
1	1,976	19.1	0	15	84	3.8
2	1,672	12.4	0	8	84	2.0
3	1,432	10.4	0	6	83	1.5
4	1,251	8.5	0	4	86	1.0

Source: NDA 22-262, CSR, Additional data provided by Applicant per FDA request.

Scheduled menstrual periods are generally light with this product as shown in Table 15.

Table 15 Scheduled Bleeding and/or Spotting Days per Cycle, ITT Cohort

Lo Seasonique Cycle	N	Mean Days	Minimum Days	Median Days	Maximum Days
1	1,802	2.5	0	2	7
2	1,547	2.3	0	2	7
3	1,351	2.2	0	2	7
4	1,199	2.4	0	2	7

Source: NDA 22-262, CSR, Adapted from Table 170, Page 642

Table 16 below provides cross-study comparisons of unscheduled bleeding and/or spotting per cycle among other approved extended cycle OCs.

Table 16 Mean Unscheduled Bleeding and/or Spotting Days per Subject-Month

Cycle	Seasonale 84 days LNG 150 mcg/EE 30 mcg + 7 days Placebo	Seasonique 84 days LNG 150 mcg/EE 30 mcg + 7 days EE 10 mcg	Lo Seasonique 84 days LNG 100 mcg/EE 20 mcg + 7 days EE 10 mcg
1	3.8	3.6	4.9
2	2.9	2.4	3.1
3	2.7	1.8	2.6
4	2.2	2.0	2.2

[1]Obtained by multiplying the appropriate 91-day cycle by 21/84
Source: Seasonale and Seasonique data taken from the Medical Officer reviews of NDA 21-544 and NDA 21-840

Medical Reviewer's Comments

- *Although cross-study comparisons have limitations and may not necessarily be valid, the bleeding/spotting profile for Seasonique is somewhat better than for the lower dose Lo Seasonique. This is not unexpected. Higher estrogen dose (30 mcg EE) OCs (Seasonale and Seasonique) generally have less unscheduled bleeding than 20 mcg EE ("low dose") OCs such as Lo Seasonique.*
- (b) (4)

Table 17 analyzes the frequency of intermenstrual (unscheduled) bleeding per cycle as reported by study subjects based on a summary of both weekly and daily diary reporting.

Table 17 Percentage of Women Taking Lo Seasonique Reporting Unscheduled Bleeding and/or Spotting

Occurrence of Unscheduled Bleeding and/or Spotting	Cycle 1 Days 1-91 % of 1802 Completers	Cycle 2 Days 92-192 % of 1547 Completers	Cycle 3 Days 183-273 % of 1351 Completers	Cycle 4 Days 274-364 % of 1199 Completers
7 or More Days	74	56	49	43
20 or More Days	40	23	17	14

Source: Additional data provided by the Applicant per FDA request.

Comparison of intermenstrual bleeding and/or spotting with Seasonique is found in Table 18.

Table 18 Percentage of Women Taking Seasonique Reporting Unscheduled Bleeding and/or Spotting

Occurrence of Unscheduled Bleeding and/or Spotting	Cycle 1 Days 1-91 % of 759 Completers	Cycle 2 Days 92-192 % of 625 Completers	Cycle 3 Days 183-273 % of 533 Completers	Cycle 4 Days 274-364 % of 446 Completers
7 or More Days	64	46	36	39
20 or More Days	29	16	10	11

Source: Adapted from Medical Officers review of NDA 21-840, Table 28.

Medical Reviewer's Comments

- *With Lo Seasonique, the occurrence of intermenstrual bleeding and/or spotting decreases markedly by the end of cycle 2 then slowly decreases over cycles 3 and 4.*
- *Bleeding and/or spotting comparisons of Seasonique and Lo Seasonique are based on separate clinical trials. No head to head trial comparing bleeding has been done. Cross-trial comparisons present limitations.*

7.1.4 Other Search Strategies

No other search strategies were used.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events (AEs) were reported during regular monthly telephone contacts and at the subject's regularly scheduled visits to the investigational site. Site personnel recorded information about AEs on the AE case report form at each clinic visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were coded according to the MedDRA dictionary by body system, organ class and preferred term. Use of the MedDRA categorization is appropriate to tabulate adverse events.

7.1.5.3 Incidence of common adverse events

Table 18 shows the incidence rates for the most frequently reported treatment-emergent adverse events (incidence rates of 5% or greater) for the Safety Cohort.

Approximately one-third of subjects reported one or more cases of headache during the course of treatment, followed by nasopharyngitis and dysmenorrhea as the three most commonly reported adverse events.

7.1.5.4 Common adverse event table

Table 19 Incidence of Treatment Emergent Adverse Events Occurring in 5% or More of Treated Subjects, Safety Cohort

Study DR-PSE-309	Lo Seasonique (N=2185)	
MedDRA Term	N	%
Nervous System Disorders		
Headache	730	33.4
Infections and Infestations		
Nasopharyngitis	358	16.4
Upper Respiratory Tract Infection	167	7.6
Sinusitis	156	7.1
Urinary Tract Infection	110	5.0
Reproductive System and Breast Disorders		
Dysmenorrhea	248	11.4
Metrorrhagia	180	8.2
Gastrointestinal Disorders		
Nausea	185	8.5
Musculoskeletal and Connective Tissue Disorders		
Back Pain	175	8.0

Source: NDA 22-262, CSR, Adapted from Table 37, Page 82

Medical Reviewer's Comments

- *The most common adverse events in the Lo Seasonique primary trial were headache (33.4%), nasopharyngitis (16.4%), and dysmenorrhea (11.3%).*
- *Although the incidence of headache with this drug seems unusually high (730 subjects or 33.4%) compared to other OCs, headache or migraine was the cause of study discontinuation in only 23 subjects (1.1%).*
- *In the Seasonique clinical trials, the most common adverse events were intermenstrual bleeding (11.44%), nasopharyngitis (7.27%), and sinusitis (6.54%). The incidence of headache in the Seasonique clinical trials was only 3.8%.*
- *In the Seasonale clinical trials, the most common adverse events were nasopharyngitis (21.9%), headache (20.6%) and menorrhagia (11.6%).*

7.1.5.5 Additional analyses and explorations

Medical Reviewer's Comment

- *Although the ITT Cohort (based on complete cycles only) was the one used primarily for assessing bleeding and/or spotting, the Division requested additional unscheduled bleeding/spotting data which was based on all subjects who received at least one dose of study medication (Safety Cohort). This data is found in Table 14 of this review.*

7.1.6 Less Common Adverse Events

Below is a summary by system organ class of all adverse events that occurred in the primary study, DR-PSE-309. There were no unexpected adverse events that occurred during the trial.

Table 20 Incidence of Treatment Emergent Adverse Events, Safety Cohort

Study DR-PSE-309	Lo Seasonique (N=2185)	
MedDRA System Organ Class	**N**	**%**
Any AE	1742	79.7
Infections and Infestations	997	45.6
Nervous System Disorders	865	39.6
Reproductive System and Breast Disorders	592	27.0
Gastrointestinal Disorders	571	26.1
Musculoskeletal and Connective Tissue Disorders	388	17.8
Respiratory, Thoracic, and Mediastinal Disorders	268	12.2
Psychiatric Disorders	248	11.3
Skin and Subcutaneous Disorders	206	9.4
Injury, Poisoning and Procedural Complications	179	8.2

Study DR-PSE-309	Lo Seasonique (N=2185)	
MedDRA System Organ Class	**N**	**%**
General Disorders and Administrative Site Conditions	175	8.0
Investigations	101	4.6
Immune System Disorders	93	4.3
Metabolism and Nutrition Disorders	37	1.7
Ear and Labyrinth Disorders	30	1.4
Eye Disorders	30	1.4
Surgical and Medical Procedures	23	1.1
Renal and Urinary Disorders	22	1.0
Vascular Disorders	20	0.9
Blood and Lymphatic System Disorders	10	0.5
Cardiac Disorders	9	0.4
Hepatobiliary Disorders	9	0.4
Endocrine Disorders	7	0.3
Pregnancy, Puerperium and Perinatal Conditions	5	0.2
Social Circumstances	4	0.2

Source: Adapted from NDA 22-262, CSR, Adapted from Table 141, Pages 543-558

7.1.7 Laboratory Findings

Laboratory tests were done at baseline and at the end of the study. Clinical laboratory included hematology (hematocrit, hemoglobin), lipid profile (cholesterol, triglycerides, LDL, HDL), liver function tests (total bilirubin, AST, ALT, alkaline phosphatase), glucose, BUN, creatinine. See Table 21 below.

Table 21 Screening and End of Study Mean Values

Test	N	Screening Mean	End of Study Mean	Mean Change from Baseline
Cholesterol (mg/dL)	1698	182.2	183.4	1.2
Triglycerides (mg/dL)	1698	105.0	107.4	2.4
LDL (mg/dL)	1690	101.3	104.2	2.9
HDL (mg/dL)	1697	59.9	58.0	-1.9
Hematocrit (%)	1653	42.0	41.7	-0.4
Hemoglobin (g/dL)	1657	13.6	13.5	-0.1
ALT (U/L)	1693	16.5	19.7	3.2
AST (U/L)	1680	18.5	20.7	2.1
Alk Phos (U/L)	1698	64.8	64.3	-0.5
Total Bilirubin (mg/dL)	1695	0.5	0.5	0.0
Glucose (mg/dL)	1692	86.5	88.1	1.6
BUN (mg/dL)	1698	11.8	11.6	-0.2
Creatinine (mg/dL)	1698	0.8	0.8	0.0

Source: Adapted from NDA 22-262, CSR, Adapted from Tables 42, 43, Pages 462-464

Medical Reviewer's Comments

- *Mean end of study changes from baseline in hemoglobin and hematocrit were negligible and not clinically significant.*
- *As would be expected in women taking a combination oral contraceptive, there were small increases in serum concentrations of total cholesterol, triglycerides, and LDL-cholesterol and a small decrease in HDL-cholesterol. Mean changes in lipids were not clinically significant.*
- *Small mean increases in ALT and AST were not clinically significant.*

Table 22 summarizes the end of study shifts in common laboratory parameters.

Table 22 Shift Analysis for Serum Chemistry, Lipid and Hematology Values

Lab	Baseline	End of Treatment						
		Low	%	Normal	%	High	%	Total
Total Bilirubin (0.2-1.2 mg/dL)	Low	5	12.5	35	87.5	0	0.0	40
	Normal	43	2.6	1,575	96.6	13	0.8	1,631
	High	0	0.0	13	54.2	11	45.8	24
	Total	48		1,623		24		1,695
ALT (6-34 U/L)	Low	1	11.1	8	88.9	0	0.0	9
	Normal	4	0.2	1,489	92.0	125	7.7	1,618
	High	0	0.0	42	63.6	24	36.4	66
	Total	5		1,539		149		1,693
AST (9-34 U/L)	Low	1	100	0	0	0	0	1
	Normal	0	0	1,573	95.6	72	4.4	1,645
	High	0	0	21	61.8	13	38.2	34
	Total	1		1,594		85		1,680
Glucose (70-115 mg/dL)	Low	1	3.6	26	92.9	1	3.6	28
	Normal	38	2.3	1,579	95.3	40	2.4	1,657
	High	0	0.0	5	71.4	2	28.6	7
	Total	39		1,610		43		1,692
Hematocrit (34-60%)	Low	1	20	4	80	0	0.0	5
	Normal	2	0.1	1,613	99.1	12	0.7	1,627
	High	0	0.0	20	95.2	1	4.8	21
	Total	3		1,637		13		1,653
Cholesterol (125-265 mg/dL)	Low	30	42.3	41	57.7	0	0.0	71
	Normal	45	3.1	1,345	91.4	81	5.5	1,471
	High	0	0.0	85	54.5	71	45.5	156
	Total	75		1,471		152		1,698
Triglycerides (36-214 mg/dL)	Low	2	9.5	19	90.5	0	0.0	21
	Normal	12	0.8	1,304	90.6	123	8.5	1,439
	High	0	0.0	132	55.5	106	44.5	238
	Total	14		1,455		229		1,698
LDL (57-186 mg/dL)	Low	89	52.0	82	48.0	0	0.0	171
	Normal	81	5.5	1,350	91.6	43	2.9	1,474
	High	0	0.0	28	62.2	17	37.8	45
	Total	170		1,460		60		1,690
HDL (33-92 mg/dL)	Low	10	41.7	14	58.3	0	0.0	24
	Normal	20	1.3	1,496	96.1	41	2.6	1,557
	High	0	0.0	73	62.9	43	37.1	116
	Total	30		1,583		84		1,697

Source: NDA 22-262, CSR, Table 45, Pages 468-473

Medical Reviewer's Comments

- *In cases where a value within the normal range at baseline rose above or below the normal range at the end of treatment, the resulting end of treatment value was close usually borderline. No end of treatment values rose to a clinically significant level.*
- *The changes observed are commonly associated with oral contraceptive use.*
- *Small increases in serum ALT, AST, and bilirubin concentrations are known effects of treatment with combined oral contraceptives.*

No additional analyses and explorations were done.

7.1.7.1 Special assessments

No special assessments were performed.

Medical Reviewer's Comments

- *Endometrial biopsies were not obtained in the DR-PSE-309 clinical trial. The Applicant has relied on the endometrial biopsy data obtained in the Seasonique clinical trials. The Seasonique dosing formulation contains 84 LNG 150 mcg/EE 30 mcg tablets followed by 7 EE 10 mcg tablets. No cases of end of study endometrial hyperplasia were found in the 181 subjects studied*
- *This Reviewer agrees that the Seasonique study (NDA 21-840, Protocol PSE-302) provides support for the endometrial safety of Lo Seasonique.*

7.1.8 Vital Signs

Vital signs (blood pressure, heart rate, weight or temperature) were obtained at screening, enrollment and at 13, 26, 39 and 52 weeks post initiation of treatment. There were no notable changes in vital signs over time within the treatment group.

Table 23 Vital Signs, Mean Change from Baseline

Study DR-PSE-309	Baseline Mean	End of Treatment	Mean Change
Mean Systolic Blood Pressure (mmHg)	111.7	112.3	0.7
Mean Diastolic Blood Pressure (mmHg)	71.0	72.0	1.1
Heart Rate	73.3	73.8	0.6
Mean Weight Gain (lbs)	158.7	160.1	1.6

Source: NDA 22-262, CSR, Table 52, Page 486

Medical Reviewer's Comments

- *There were no significant changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, or weight) over time.*
- *There were no clinically significant abnormalities in vital signs that occurred during the trial.*
- *Although headache occurred in 33% of the patients taking Lo Seasonique, there was no indication of unusual blood pressure elevations related to the use of this drug.*

7.1.8.1 Additional analyses and explorations

No additional analyses and explorations were done

7.1.9 Electrocardiograms (ECGs)

No ECGs were performed at screening or during the phase 3 clinical trial.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Class labeling for OCs discusses potential associations with malignancies (breast, cervix).

7.1.12 Special Safety Studies

No special safety studies were performed for this NDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no known withdrawal or abuse potential for LNG/EE.

7.1.14 Human Reproduction and Pregnancy Data

No human reproduction or pregnancy data was required for this NDA. No fetal or maternal toxicity has been attributed to the LNG/EE combination therapy found in oral contraceptives.

7.1.15 Assessment of Effect on Growth

No assessments regarding growth effects were included in this NDA submission.

7.1.16 Overdose Experience

The potential for either intentional or accidental overdose with Lo Seasonique is not expected to be any different than that of any other combined oral contraceptive.

7.1.17 Postmarketing Experience

There is no postmarketing experience with this extended cycle low dose (EE 20 mcg) oral contraceptive because it is not marketed anywhere in the world. However, there is extensive postmarketing experience with the 28-day combination OC formulations containing LNG 100 mcg/EE 20 mcg since 1997 and with the higher dose LNG 150 mcg/EE 30 mcg formulation since 1982. No worrisome safety signals have emerged from this extensive postmarketing experience.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 2,185 subjects received at least one dose of study drug during this primary clinical trial. Of these, 1,249 subjects completed the one year trial.

7.2.1.1 Demographics

The demographics for Study DR-PSE-309 are presented in Table 24.