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RESEARCH**

APPLICATION NUMBER:

21-840

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-840
Submission Code	000 – Complete Response
Letter Date	March 24, 2006
Stamp Date	March 27, 2006
PDUFA Goal Date	May 27, 2006
Reviewer Name	Ronald J. Orleans, M.D.
Review Completion Date	May 25, 2006
Established Name	Levonorgestrel/ethinyl estradiol; ethinyl estradiol
Trade Name	Seasonique™
Therapeutic Class	Oral contraceptive
Applicant	Duramed Pharmaceuticals, Inc
Priority Designation	S
Formulation	Tablet
Dosing Regimen	One tablet daily administered as 91-day cycles. Each cycle consists of 84 (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) tablets followed by 7 (ethinyl estradiol 0.01 mg)
Indication	Prevention of pregnancy
Intended Population	Women at risk for pregnancy who desire contraception

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval of Seasonique™ for prevention of pregnancy is recommended based on the Applicant's demonstration of acceptable efficacy (Pearl Index of 1.77), an acceptable safety profile for an effective oral contraceptive, and submission of acceptable labeling.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

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

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

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7. Integrated Review of Safety

7.2.9 Safety Update

7.2.9.1 Update of Clinical Studies

The Applicant has submitted a safety update in a paper submission dated March 24, 2006. This safety update consists of an interim clinical study report for Duramed study PSE-304 entitled, "A Parallel, Multicenter, Open-Label Study to Evaluate the Safety of an Extended Cycle Combination Oral Contraceptive, DP3-84/10, Which Utilizes Ethinyl Estradiol During the Pill-Free Interval For Prevention of Pregnancy in Women" dated January 12, 2006. This interim study report only contains safety data from the ongoing PSE-304 clinical study. The study period included in this interim report is May 22, 2003 to July 31, 2005. The study drugs in study PSE-304 are:

- DP3-84/30 which is levonorgestrel 0.15 mg/ethinyl 0.03 mg tablets given for 84 days followed by ethinyl estradiol 0.03 mg given for seven days and
- DP3-84/10 which is levonorgestrel 0.15 mg/ethinyl 0.03 mg tablets given for 84 days followed by ethinyl estradiol 0.01 mg given for seven days. This is the Seasonique formulation.

The primary objective of this study is to evaluate the safety of DP3-84/10 (Seasonique) taken for up to an additional three consecutive years as a Phase III extension study in women who participated in the original one year studies PSE-301 or PSE-302. Subjects enrolled in PSE-301 and PSE-302 were women between 18-45 years of age who desired pregnancy prevention.

Subjects enrolled in PSE-304 initially received either DP3-84/30 or DP3-84/10. Following review of the completed Phase III primary studies, all subjects participating in PSE-304 were switched to DP3-84/10 for the duration of their participation in PSE-304. A total of 317 subjects were treated in PSE-304. The first subject began therapy on May 25, 2003 and the last began on December 7, 2004. A total of 116 subjects have discontinued with 201 subjects still on treatment. As of the July 31, 2005 data cut-off, 240 subjects (75.7% of 317) have completed one year of treatment and 43 (13.6% of 317) have completed two years of treatment. The submitted interim report includes exposure for a total of 798 DP3-84/30 and 909 DP3-84/10 complete 91-day cycles, corresponding to 2,708 and 3,093 28-day cycles, respectively, or a combined total of 5,801 28-day cycles.

Death

No deaths were reported in this study.

Serious Adverse Events

Ten serious adverse events have been reported with no reported VTEs. See Table 1.

Table 1 Serious Adverse Events, Study PSE-304

Treatment Group	Serious AE	Severity	Relationship to Study Medication	Subject Discontinues Due to SAE?
DP3-84/30	Chest Pain	Moderate	None	Yes
	Spontaneous Abortion	Severe	None	No
	Myocardial Infarction	Mild	Possible	Yes
	Appendicitis	Severe	None	No
DP3-84/10	Sialoadenitis	Moderate	None	No
	Enlarged Lymph Gland Left Axilla	Moderate	None	No
	Acute Cholecystitis	Severe	Possible	No
	Gall Stones	Unknown	None	No
	Lumbar Disc Damage	Severe	None	No
	Gall Stones	Severe	Possible	No

Source: PSE-304 Interim Clinical Study Report, Page 52

Subject 0001-0203 was a 36 year old Caucasian non-smoker. She began taking DP3-84/30 on July 21, 2002 and continued during PSE-304. At her study visit on April 14,

2005, the subject reported that she had recently been hospitalized for the evaluation of chest pain. She also reported that she had been experiencing "dull chest pain" (which she had never reported) for years. On _____, she went to the Emergency Department complaining of left sided chest pain radiating to her left arm for greater than one hour. She was admitted for observation and work-up. Her physical examination and cardiac evaluation including electrocardiogram, echocardiogram, and cardiac enzymes were normal. In addition, pulmonary embolism was also ruled out.

Subject 61-0441 was a 40 year old Caucasian female. She was a prior smoker having quit in 2002. The subject completed PSE-302 and was enrolled in the extension study, PSE-304, on September 25, 2003. She began taking DP3-25/30 on September 29, 2002 and was assigned to DP3-84/30 in PSE-304, which she began taking on September 28, 2003.

The subject completed a lifeguard recertification program, which included a high-exertion swimming test, on _____ . That night, she awoke with chest pressure radiating to her left arm. She presented to the Emergency Department on _____ approximately two hours after onset of the pain, and was admitted to the hospital. Her chest pain was relieved with sublingual nitroglycerine.

She underwent a complete work-up and myocardial infarction was diagnosed based on cardiac enzyme results: total CPK 669 U/L (30-165), MB-CPK 66 ng/mL (0-0.5), troponin 10 ng/mL (0-0.4). Blood pressure was normal as was the electrocardiogram. Echocardiogram and cardiac catheterization were also normal. Cholesterol was 206 mg/dL, HDL 55 mg/dL, LDL 136 mg/dL.

Her discharge diagnosis was non-Q wave myocardial infarction probably secondary to coronary spasm. She was discharged in good condition on _____

Adverse Events

Since this is an on-going trial, only treatment-emergent adverse events occurring between the PSE-304 first dose date to July 31, 2005 were included in the interim report. A total of 69 (46.9% of 147) subjects in the DP3-84/30 group reported at least one AE while 87 (51.2% of 170) subjects in the DP3-84/10 group reported at least one AE. The overall incidence of adverse events, especially those known to be associated with oral contraceptive, use were not observed to have increased in this extension study when compared to the primary PSE-301 study. The most common adverse event classified under the Reproductive System and Breast Disorders was metrorrhagia which occurred in nine of 170 subjects taking DP3-84/10 (5.29%) and seven of 147 subjects taking DP3-84/30 (4.76%). A total of 22 subjects (6.9% of the 317 treated) discontinued the study due to adverse events, nine subjects due to some reported bleeding and/or spotting event. Five of these were in the DP-84/30 group and four were in the DP3-84/10 group.

Clinical Laboratory Evaluation

No notable changes in serum chemistry were found. Changes in the lipid panel were not clinically significant.

7.2.9.3 Reviewer's Conclusion

Based on the data available from the July 31, 2005 data cut-off date analyzed for this interim study report, overall rates of study discontinuation, the incidence of adverse events (including serious adverse events and adverse events leading to study discontinuation) are consistent with those observed in study PSE-301 and PSE-302 and support the long-term safety of the Seasonique regimen. There is also no substantial change in the incidence of common, but less serious adverse events between the new data and the original NDA data.

The serious adverse events listed in Table 1 that are possibly related to study medication i.e., gall bladder adverse events and myocardial infarction are known to be associated with oral contraceptive use.

The Applicant has informed the Division that Seasonique™ is not marketed in other countries so that there is no worldwide experience relating to the safety of this drug.

9.4 Labeling Review

The Applicant's proposed labeling submitted during the original review cycle was reviewed by the Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Medication Errors and Technical Support (DMETS).

Labeling Recommendations

Labeling recommendations were made by DDMAC on March 1, 2005. Seventeen recommendations were received.

- **CLINICAL PHARMACOLOGY:** Four recommendations were addressed by Clinical Pharmacology.
- **INDICATIONS AND USAGE:** Several recommendations concerning the Applicant's derived Pearl Index became moot with the acceptance by the Applicant of the recalculated Pearl Index of 1.77. Other minor editorial recommendations were addressed.
- **WARNINGS:** Two recommendations were considered.
- **ADVERSE EXPERIENCES:** Four recommendations were discussed. The header was changed to "ADVERSE REACTIONS" for consistency.

- DOSAGE AND ADMINISTRATION: One recommendation was submitted.
- REFERENCES: One recommendation to delete this section was considered.
- Brief Summary Patient Package Insert and DETAILED PATIENT LABELING: Several recommendations were submitted.
- Carton and Container Labels: “Promotional labeling” was discussed.

Medical Officer’s Comments

- *The above recommendations made by DDMAC were carefully reviewed by the Division and incorporated where appropriate.*
- *Acceptable labeling was submitted by the Applicant on May 24, 2006.*

Division of Medication Errors and Technical Support (DMETS)

The following recommendations were submitted by DMETS on April 14, 2006:

- DMETS does not recommend the use of the proprietary names, Seasonique, ~~Seasonale~~ or ~~Seasonale~~. The primary concern related to the possible look-alike and/or sound-alike confusion with Seasonale.
- On the commercial product, DMETS recommends using an entirely different color scheme to differentiate Seasonique from Seasonale. They also recommend removing the four dot logo and differentiating the names more prominently to ensure that the potential for confusion is minimized.
- DMETS recommends the removal of the terminology “extended-cycle” because it may imply an additional benefit over other oral contraceptive tablets or dosing schedules.

Medical Officer’s Comments

- *The above recommendations made by DMETS were carefully reviewed by the Division.*
- *The Division elected to allow the Applicant to keep the name “Seasonique” for the drug product. Confusion with the name “Seasonale”, even if it should occur, would not result in a clinically significant problem.*
- *The Division believes that the color scheme for the carton found in the product labeling for Seasonique is sufficiently different from that for Seasonale® that dispensing errors due to carton similarities are not likely to occur.*
- *The Division elected to allow the Applicant to retain the term “extended cycle” on the blister label and carton labeling. The term “extended cycle” appropriately*

describes the drug product dosage regimen (91-day cycle) as opposed to a 28-day product and is consistent with the blister label and carton labeling for Seasonale®.

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MEMORANDUM

DATE: April 5, 2006

FROM: John K. Jenkins, MD
Director, Office of New Drugs

TO: NDA 21-840

SUBJECT: January 6, 2006, Formal Dispute Resolution Request

This memorandum is written to describe my rationale for granting the formal dispute resolution submitted by the sponsor regarding the approvable letter issued by the Division of Reproductive and Urology Products on August 17, 2005. My action on that appeal occurred on March 16, 2006, and this memorandum is submitted to complete the administrative record.

In considering the sponsor's appeal the primary issue was whether the addition of 7 days of estrogen during the hormone free period (HFP) of the existing extended-cycle oral contraceptive (i.e., Seasonale) must be "justified" beyond a showing that the product is safe and effective for its intended use; the prevention of pregnancy. The Division and ODE expressed legitimate concern regarding the potential impact of the additional estrogen on the safety profile for the product given the established dose-related link between exogenous estrogen use and adverse effects. To address this concern they requested additional data to demonstrate a "clinically meaningful benefit" of the estrogen during the HFP to offset the potential risk. Such information would clearly be of value to assist healthcare providers and patients in making decisions regarding selections among the various available hormonal contraceptives (i.e., why use Seasonique instead of Seasonale). The key regulatory question, however, is whether the additional data are required to establish the safety and effectiveness of the product in support of approval under our statutory and regulatory framework for new drug approvals.

While the data requirements for approval are by necessity informed by judgment on the part of the Agency official making the decision, they are also informed by established Agency policies, guidance, and precedents for development in a particular area. In the current case, it appears clear that the established standards for approval of a hormonal contraceptive were met by the data submitted in the original NDA (i.e., an adequate number of women exposed for an adequate duration, an acceptable rate of pregnancy on therapy as measured by the Pearl Index, and an acceptable safety profile). While the sponsor clearly hoped to be able to market Seasonique as offering benefits over Seasonale, no head-to-head comparative study was performed, and thus no claims can be supported. Of note, the Division did not request a comparative trial, which would have been the ideal vehicle for establishing added clinical benefit of the estrogen during the HFP, and specifically told the sponsor during a pre-NDA meeting that the development program "would not support labeling or advertising claims regarding the clinical significance of the 7 days of additional ethinyl estradiol." The Division's request for additional data as cited in the AE letter would have been strengthened had this issue been raised with the sponsor during interactions prior to submission of the NDA.

With regard to the issue of the dose of estrogen in hormonal contraceptives, there has clearly been a trend toward lowering the daily and cumulative estrogen exposure in an attempt to minimize the risk to the patient. While that trend is clear in the practice of medicine, I have not been able to uncover evidence of Agency policy or guidance requiring establishment of the lowest effective

dose of estrogen in support of approval of hormonal contraceptives. In fact, hormonal contraceptives with higher doses of estrogen than contained in Seasonique, both daily and cumulative, continue to be available as FDA approved products and have not been the subject of regulatory action. Further, FDA has in recent years approved hormonal contraceptives with higher daily or cumulative doses of estrogen than other approved products (as was the case with the approval of Seasonale in 2004) without a requirement that the higher dose be specifically "justified" by additional data beyond that required for approval of an oral contraceptive in general. Finally, FDA recently became aware that a hormonal contraceptive transdermal patch product results in a 60% higher exposure to estrogen than previously thought. FDA alerted healthcare providers and patients to that new information, but did not initiate regulatory action to withdraw the product on the basis of safety.

If the FDA had established a policy that clearly articulated a need for sponsors to limit estrogen doses in hormonal contraceptives to the lowest effective dose, or to provide data to support the "clinically meaningful benefit" of a higher dose to improve the safety of hormonal contraceptives, the Division's position with regard to Seasonique would be strengthened. In fact, it appears that the Agency has recognized the value of having a range of approved hormonal contraceptive products so that healthcare providers and patients can choose the product that meets the particular needs of an individual patient. Given the established precedent, I do not believe a requirement for additional data beyond that normally required for approval of a hormonal contraceptive can be supported for Seasonique. I believe that the potential for increased risk related to the increased exposure to estrogen can be communicated to healthcare providers and patients in the labeling to allow for an informed use decision in comparison to other available products. As noted earlier, no comparative claims have been established for Seasonique and the labeling and promotion should not suggest such benefits compared to Seasonale or other hormonal contraceptives.

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**Division Director Memorandum
SEASONIQUE**

NDA:	21-840
Drug:	SEASONIQUE™
Dosage Form/Route:	Tablet/Oral
Strength:	0.15 mg levonorgestrel (LVG)/ 0.030 mg ethinyl estradiol (EE) - Days 1-84 0.01 mg ethinyl estradiol -Days 85 - 91
Applicant:	Duramed Pharmaceuticals, Inc.
Original Submission Date:	October 21, 2004
Medical Officer Completion Date:	
Date of Memorandum:	August 17, 2005

1.0 Background

In this application, the Sponsor is seeking approval for a 91-day extended cycle regimen of an oral contraceptive combination of levonorgestrel (LVG) and ethinyl estradiol (EE). This is the 2nd extended cycle regimen drug product that is sought by the Sponsor. The first formulation, SEASONALE®, received Approval on September 5, 2003. The formulations for SEASONIQUE™ and SEASONALE® are identical for Days 1-84 (the active therapy days); both formulations employ 0.15 mg of LNG in combination with 0.03 mg of ethinyl estradiol. With SEASONIQUE™ the Sponsor has replaced the placebo tablets, in the SEASONALE® formulation, with 0.010 mg of ethinyl estradiol for days 85-91. The Sponsor :

NDA 21-840 for SEASONIQUE™ was submitted by Duramed on October 21, 2005. It was administratively filed on December 14, 2005. In the 74 day letter to the Sponsor, which is sent to notify the Sponsor of any noted or potential deficiencies, the Division stated "Given the known risks associated with exogenous estrogen use in combined oral contraceptives for women of reproductive age, the Division will be looking very carefully to evaluate whether the addition of 10 micrograms per day of ethinyl estradiol for the seven days of the previous hormone free period of a 91-day regime (SEASONALE®) provides sufficient clinical benefit to the patient using SEASONIQUE™ to justify risk."

2.0 Data in the NDA Submission

2.1 Contraceptive efficacy: Two one-year, Phase 3, randomized, multicenter, open-labeled studies were submitted to support the efficacy and safety of SEASONIQUE™.

Study PSE-301 was the primary study. For this study, 2,049 subjects were randomized to receive either DP3-84/10 (SEASONIQUE™; 1,025 women randomized) or DP3-84/30 (.030 mg EE days 85-91, 1,024 women randomized). No regulatory claims are being sought for DP3-84/30 based on this application. The Pearl Index for SEASONIQUE™ as calculated by the FDA statistician, based on seven “on-treatment” pregnancies, was determined to be 1.77 (95% CI 0.71, 3.64).

Study PSE-302 was a randomized (1:1:1:1), 4-armed, multicenter, open-label, Phase 3 clinical trial conducted to provide supportive information on safety, including endometrial safety data, and efficacy. For this study, 380 subjects were randomized to receive either DP3-84/10 (SEASONIQUE™; 95 subjects randomized), DP3-84/30 (96 subjects randomized), or two monthly regimens. However, the clinical reviewing team notes that there were too few completed cycles to calculate accurate Pearl Indices for any of the drug products in this study.

The overall opinion of the clinical review team is that SEASONIQUE™ is efficacious for pregnancy prevention.

2.2 Unscheduled bleeding: The most informative measure of cycle control is the assessment of the number of days of unscheduled bleeding (i.e. non-withdrawal bleeding). For the first (91-day) cycle of use, there was a mean of 14.4 days of unscheduled bleeding and/or spotting on SEASONIQUE™. This compared to a mean of 2.4 for the first cycle of use of Nordette (.15mg LVG/0.30mg EE (28-day)). After the 2nd cycle of use (182 days), the mean number of unscheduled days of bleeding and/or spotting was 9.5 days for SEASONIQUE™ compared to 1.5 days in the 6th cycle (168 days) of use of Nordette. By the end of the 4th cycle of use (364 days), the mean number of days of unscheduled bleeding and spotting was 7.8 with SEASONIQUE™.

Per the Applicant’s analysis of subjects completing cycle 1 of treatment with SEASONIQUE™, 65% had 7 or more days of unanticipated bleeding and or spotting recorded in their diary. Twenty-Nine percent (29%) had 20 or more days of unanticipated bleeding. By the end of the fourth cycle (364 days of treatment), 40% of subjects still experienced 7 or more days of unanticipated bleeding and 12% experienced greater or equal to twenty days.

There are significant concerns regarding the lack of cycle control in the form of unanticipated bleeding demonstrated in subjects treated with this drug product.

2.3 Hormone related symptoms: The study of hormone-related symptoms was not incorporated into the study design for either study (PSE-301 or PSE-302) submitted in this NDA. Treated subjects were not required to qualify for entry into the study based on any minimum severity criterion for any particular hormone-related symptom or symptoms. Each subject did make a daily record, in an electronic diary, of the existence and severity of acne, headache, fatigue, bloated ness, breast tenderness, swelling in hands/ankles, migraine headache, cramps/pelvic pain, muscle/joint pain, and back pain. In addition, the existence and severity of feelings or a mood of: depression/hopelessness, anxious/tenseness, sadness/tearfulness, or anger/irritability was recorded on a VAS scale by the subject in the daily electronic diary.

The Applicant submitted with this NDA a list of graphs which tracked each of the above symptoms through treatment, based on the information obtained in the daily diaries. Each graph illustrated the percentage of all treated subjects (Safety cohort) reporting a particular symptom. The Applicant concluded that no consistent systematic changes in any of these hormone-related symptoms were observed through treatment. Further, the Applicant concludes that "results need to be further explored".

3.0 Conclusions

SEASONALE®™ is the only approved extended cycle oral contraceptive. The Sponsor, Duramed/Barr received approval to market this drug product on September 5, 2003. The Applicant for SEASONIQUE™ (Duramed) _____

_____ relative to the previously approved product, SEASONALE®, which has no active drug product during the 85-91 day "hormone-free" interval.

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4. Regulatory Action:

I agree with the secondary reviewer (medical team leader) that NDA 21-840 is Approvable because of the following deficiency:

The application for the Seasonique™ extended cycle contraceptive regimen (consisting of 150 micrograms levonorgestrel and 30 micrograms ethinyl estradiol administered for 84 days and 10 micrograms ethinyl estradiol administered days for days 85-91) did not provide clinical trial data that demonstrated benefit of the addition of 10 micrograms of ethinyl estradiol per day on days 85-91 to this extended cycle contraceptive regimen compared to the exact same regimen that has placebo during days 85 to 91. Because of the known risks of exogenous estrogen, replacement of placebo by ethinyl estradiol to this regimen cannot be supported without demonstration of a clinically meaningful benefit to the patient.

To address this deficiency, a randomized controlled clinical trial that demonstrates that the addition of 10 micrograms of ethinyl estradiol to the previous hormone free period : _____



_____ should be conducted. The full details of such a trial and what clinically meaningful benefit is to be demonstrated should be discussed with the Division prior to initiation.

Daniel A. Shames MD FACS
Director,
DRUP/CDER/FDA

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CLINICAL REVIEW

Application Type NDA
Submission Number 21840
Submission Code 000

Letter Date October 21, 2004
Stamp Date October 21, 2004
PDUFA Goal Date August 19, 2005

Reviewer Name Ronald J. Orleans, M.D.
Review Completion Date August 16, 2005

Established Name Levonorgestrel/ethinyl
estradiol; ethinyl estradiol
(Proposed) Trade Name Seasonique™
Therapeutic Class Oral contraceptive
Applicant Duramed Pharmaceuticals, Inc.

Priority Designation S

Formulation Eighty-four levonorgestrel 0.15
mg/ethinyl estradiol 0.03 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 Seasonique™ for prevention of pregnancy is recommended based on the Applicant's demonstration of an acceptable Pearl Index and an acceptable safety profile. Approval is contingent on agreements with the Applicant concerning product labeling. It should be clearly stated in the label that _____

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 Seasonique. No specific risk management steps are recommended.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Duramed Pharmaceuticals, Inc. has proposed a new type of extended cycle oral contraceptive be approved for the indication of prevention of pregnancy. To seek approval for this regimen, the Applicant has submitted a NDA (NDA 21-840) under Section 505(b)(2). Their application consists of two multicenter studies that provide the information supporting the claims for safety and efficacy of Seasonique. The primary study, PSE-301, was designed to provide adequate evidence supporting the efficacy and overall safety of DP3-84/10 (Seasonique), and the smaller supportive study, PSE-302 was designed to obtain baseline and end of treatment endometrial biopsy data on all treated subjects. Both studies included two 91-day extended regimen DP3 arms. DP3-84/30 consisted of 84 days of active treatment with the combination drug levonorgestrel 150 mcg and ethinyl estradiol 30 mcg followed by seven days of ethinyl estradiol 30 mcg monotherapy, administered orally for four 91-day cycles. DP3-84/10 consisted of 84

days of active treatment with the combination drug levonorgestrel 150 mcg and ethinyl estradiol 30 mcg followed by seven days of ethinyl estradiol 10 mcg monotherapy, administered orally for four 91-day cycles. The PSE-302 study design also incorporated two additional 28-day arms for comparison: DP3-25/30, which consisted of 25 days active treatment with the combination drug levonorgestrel 150 mcg. and ethinyl estradiol 30 mcg followed by three days of ethinyl estradiol 30 mcg monotherapy, and commercially available Nordette which consisted of 21 days active treatment with the combination drug levonorgestrel 150 mcg. and ethinyl estradiol 30 mcg followed by seven days of placebo. Neither of the two clinical studies submitted in this NDA used Seasonale as a comparator.

1.3.2 Efficacy

Efficacy was based on the ability of Seasonique to prevent pregnancy in the Phase 3 clinical trial. This was calculated by the Pearl Index (PI) using all “On-treatment” pregnancies. On-treatment pregnancies are defined as those for which conception occurs on or after the date of first taking study drug and extends through the 14 days following the last dose of study drug.

The most conservative approach to calculate the Pearl Index was employed. Only women age 18-35 were used in the calculation. All incomplete cycles (less than 91 days) and all cycles with additional birth control methods were excluded from the calculation. These criteria affect the denominator in the Pearl Index calculation.

As determined by the medical reviewer, the total number of “On-treatment” pregnancies was seven. The Pearl Index for Seasonique based on 5125.25 patient-months of use was calculated by the FDA statistician to be 1.77 per 100 women-years of use. Although a minimum of 10,000 28-day cycles is usually studied for new oral contraceptives, this is an approved contraceptive formulation dose (approved since 1982) that only differs in the dosing duration. The 5125.25 patient-months is therefore considered sufficient for efficacy. Compared to the Pearl Index for other approved combination oral contraceptives (which has been as high as 2.39 in Phase III clinical trials), a Pearl Index of 1.77 is acceptable.

Theoretically, the use of extended combination oral contraceptives, may increase pregnancy protection for some patients. There are two less time periods for withdrawal hormone effects during each Seasonique cycle so that so called “escape” ovulation may be less likely. There do not appear to be any theoretical reasons why extended oral contraceptive therapy should provide less pregnancy protection than conventional 28-day dosage regimens. There also does not appear to be any theoretical reason why Seasonique should be any less effective in preventing pregnancy than Seasonale which has a Pearl Index of 1.98 per 100 women-years of use. However, no objective evidence was presented in the submission to support the theory.

The contraceptive efficacy of Seasonique is acceptable.

1.3.3 Safety

The safety database for DP3-84/10 (Seasonique) involves 1006 subjects (ITT) in the primary PSE-301 study and 95 subjects in the PSE-302 endometrial safety study. In addition, 1013 subjects in the DP3-84/30 arm of Study PSE-301 and 95 subjects in the DP3-84/30 arm of PSE-302 were studied in the safety cohort.

Duramed did not submit any new nonclinical pharmacokinetic or toxicology studies in support of the current application. The Applicant concluded that the safety of Seasonique could be adequately demonstrated without additional nonclinical studies, because sufficient data relating to the safety of Seasonale already existed and this data also supports the safety of the new Seasonique dosing regimen. It was felt by the Applicant that the “minor” difference of replacing the placebo tablets in Seasonale with the ethinyl estradiol 10 mcg tablets in Seasonique did not impact on the safety profiles of the combination tablets of levonorgestrel and ethinyl estradiol.

The safety data base for DP3-84/10 (Seasonique) in NDA 21-840 consisted of 1101 subjects. Of these, 546 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 to date from the Seasonique primary trial or from the Seasonique endometrial protection study.

The contraceptive safety of Seasonique is acceptable.

1.3.4 Dosing Regimen and Administration

Dosing duration is the key difference in this combination oral contraceptive application. Active combination oral contraceptive tablets are being given for 84 days instead of 21 days. This regimen was previously approved with Seasonale. In addition, a seven day course of monophasic estradiol tablets have replaced the classical “placebo” tablets.

1.3.5 Drug-Drug Interactions

No analyses of drug-drug or drug-disease interactions were performed. Concomitant medication information, however was collected throughout the study.

1.3.6 Special Populations

Combination oral contraceptives are intended for the population of women at risk for pregnancy. No formal pharmacokinetic studies of Seasonique™ were performed in different racial groups. No formal studies evaluated the effect of hepatic or renal disease on the disposition of Seasonique. The fact that steroid hormones may be poorly metabolized in patients with impaired liver function is already part of class labeling for oral contraceptives.

The Applicant has requested a full waiver of all pediatric studies since according to class labeling, the safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age and are expected to be the same for post pubertal adolescents under the age of 16 and for 16 years and older. A waiver is 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-, (17 α)-, (-)-. The chemical name for EE is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-. The proposed trade name is Seasonique™. Seasonique is a 91-day “extended cycle” oral contraceptive containing 84 tablets of the same combination LNG 0.15 mg and EE 0.03 mg followed by seven tablets of EE 0.01 mg 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 oral contraceptive products containing LNG and EE have been marketed for decades worldwide and in the United States since 1968. When oral contraceptives were first introduced, the dosage regimen was designed to induce withdrawal bleeding every 28 days. This 28-day regimen 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 withdrawal periods.

Off-label extended use of numerous types of oral contraceptives has been employed clinically for many years. For decades, clinicians have at times advised patients to omit placebo pills in their oral contraceptive regimens and extend the active pills for either medical reasons (e.g. for endometriosis) or social reasons (e.g. wishing to avoid menses when on honeymoon) reasons.

Seasonale® is the first and only extended cycle oral contraceptive approved by the FDA (September 5, 2003). Seasonale is a combination oral contraceptive that contains 0.15 mg LNG and 0.03 mg EE 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 withdrawal menstrual periods to four per year in contrast to 13 menstrual periods per year as occurs with a conventional 28-day cycle oral contraceptive.

Seasonique like Seasonale is an extended cycle oral contraceptive. Seasonique is a 91-day extended cycle oral contraceptive containing 84 tablets of the same combination LNG 0.15 mg and EE 0.03 mg followed by seven tablets of EE 0.01 mg monotherapy instead of seven days placebo. The Applicant purports that Seasonique is a highly efficacious oral contraceptive with a bleeding profile that is better than Seasonale. The focus of this review will be to find objective evidence for this statement.

Mircette® (NDA 20-713) was the first approved combination oral contraceptive to use a shortened placebo interval. The Mircette regimen consists of administering 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 not administering EE 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.

2.3 Availability of Proposed Active Ingredient in the United States

The combination of 0.15 mg LNG and 0.03 mg EE is the same dosage as that contained in each active tablet of Nordette, a combination oral contraceptive approved for marketing by the FDA in May, 1982, and now marketed by Monarch Pharmaceuticals. This LNG/EE combination is also the same dosage strength found in each active tablet of Portia, the generic version of Nordette that is marketed by Barr Laboratories. Duramed Research, Inc., the current Applicant for this NDA, is a subsidiary of Barr Pharmaceuticals, Inc.

There are approximately 21 different brands of combination oral contraceptives containing LNG/EE currently approved in the United States (See Section 10.1.1.1).

2.4 Important Issues With Pharmacologically Related Products

Important issues with oral contraceptives 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. In the last ten years, epidemiological studies have also focused on newer progestins in relation to thromboembolic disorders.

As women progress through their reproductive years, some are vulnerable to changes in hormone levels resulting in symptomatology that may cause a significant decrease in quality of life. One method of managing symptoms during the hormone-free interval is extending the number of weeks before it, as Seasonale does. Presently, however, there is no oral contraceptive regimen

that completely eliminates the hormone-free interval. The Applicant _____ h

✓

✓

Medical Reviewer's Comment

- *The Applicant admits there is limited data available regarding _____ immediately following exposure to extended cycle oral contraceptive regimens. Of interest though is that when oral contraceptives were first developed, a therapeutic application was for the treatment of _____ It is doubtful however, if any objective clinical trial evidence supported this practice.*

Medical Reviewer's Comment

- *NDA 21-840 is seeking an indication solely for the prevention of pregnancy. The Applicant makes general statements in the submission that shortening or eliminating the hormone free interval can* _____

No head to head trials with the already approved Seasonale were included in this NDA. Therefore, the main questions for this reviewer will be:

1. *Is the product safe and effective as an oral contraceptive?*
2. *Does the substitution of EE 0.01 mg for placebo have any added benefit or risk with regard to safety or efficacy?*
3. *Should the product be approved if safety and efficacy are similar to that of the already approved Seasonale which has less total ethinyl estradiol?*
4. *If the product is safe and effective as an oral contraceptive, should the new formulation be approved because it represents a new approach to oral contraception in spite of the fact that the total estrogen in this formulation may be slightly higher?*

2.5 Presubmission Regulatory Activity

The Applicant submitted IND 63,735 on November 30, 2001. After a review of this submission, several concerns were communicated to the Applicant via a letter sent to Barr Laboratories dated January 10, 2002. The major concerns were as follows:

- The Division stated in this letter that to demonstrate the contraceptive efficacy and safety of the new treatment regimens DP3-84/30, DP3-84/10, and DP3-25/30, the total number of patients proposed in Protocols PSE-301 and PSE-302 are inadequate to support an NDA submission. Ten thousand women-months of use and 200 women completing a one year treatment period with product use are required for approval of a new contraceptive drug product.
- It was recommended that study subjects be followed post-study to determine return of fertility as well as resumption of normal menses.

- Discontinuation of study treatment and discontinuation from the study should be reported in two ways. First, the overall discontinuation rates should be reported for each study arm. Second, the reason-specific discontinuation rates should be reported for each discontinuation reason for each study arm.
- Further recommendations were made regarding pregnancy rate calculations:
 1. Pregnancy should be defined as a positive pregnancy test, regardless of ultrasound findings.
 2. Conception date should be calculated considering sonogram data, quantitative HCG, qualitative HCG, pelvic examination, delivery date, and weight and gestational age assessment of infant at birth.
 3. If a conception clearly occurred before the first date of taking the study drug, then it should not be counted as a “during” treatment pregnancy.
 4. If a conception clearly occurred more than 14 days after the last date of the study drug, then it should not be counted as a “during” treatment pregnancy.
 5. If it is unclear exactly when the conception occurred, then it should be counted as a “during” treatment pregnancy.
 6. The “during” treatment pregnancy rates should be calculated both for perfect-use pregnancy rate and typical-use pregnancy rate in all subjects up to age 35 at first date of taking the study drug, as well as in all subjects of any age, utilizing Pearl Index and life table analyses.
 7. If a subject uses a birth control method (BCM) other than the study oral contraceptive, those cycles when the additional BCM was used should be eliminated from the denominator for pregnancy rate calculations.

In a subsequent letter to Barr dated February 7, 2002, the Division commented on the number of endometrial biopsies needed to establish safety:

- “We consider it adequate to establish gynecologic safety if a total of 80 evaluable sets of endometrial biopsies are submitted for Study PSE-302, 40 sets in the DP3-84/30 group and 40 sets in the DP3-25/30 group. One biopsy of each set should be obtained at baseline and a second biopsy from the same subject after one year of treatment.”
- “We consider a total of two endometrial biopsies per subject in Study PSE-302 to be reasonable, one at baseline and the other after one year of treatment.”

At the Pre-NDA meeting of August 30, 2004, the Division concurred with Barr’s plan to file an NDA for the DP3-84/10 dosage strength for the indication of prevention of pregnancy only. Additional agreed upon points included:

- Efficacy calculations (both Pearl Index and life table analyses) should include analyses based on the population 18 to 35 years of age and who used no other form of contraception. Two sided, 95% confidence intervals for the point estimates should also be provided.

- The Applicant should be able to ensure that the electronic diary data collected was accurate and entered by the subject.

The following additional statistical comments were later forwarded to the Applicant:

- Provide the following additional analyses:
 1. A global Pearl Index and life table estimate using all cycles and all patients, regardless of use of another form of birth control.
 2. A Pearl Index and life table estimate using all cycles and all patients from 18 to 35 years of age.
 3. Life table estimates based on a 91-day cycle interval and a 28-day cycle interval for the 91-day treatment cycles.

2.6 Other Relevant Background Information

At the Pre-NDA meeting of August 30, 2004, the Division voiced no objection to the Applicant's plan to file an NDA for the DP3-84/10 dosing regimen containing 0.01 mg EE monotherapy for the prevention of pregnancy. The claim would only be for the prevention of pregnancy because

There was no
mention made at this meeting that the Applicant would be better served if Seasonale were used as a comparator drug or that some other benefit
would need to be demonstrated regarding the EE
monotherapy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The following initial deficiencies identified by the FDA reviewing chemist were satisfactorily resolved by the Applicant:

1. Provide additional stability data when it is available.
2. Confirm the Master Batch Formula for the manufacture of each type of tablet used in clinical and/or stability studies. Indicate the presence or absence of an overage for either of the active pharmaceutical ingredients (levonorgestrel, ethinyl estradiol).
3. Submit a Letter of Authorization for DMF

3.2 Animal Pharmacology/Toxicology

There are no significant review issues with Pharmacology/Toxicology. No pharmacology/toxicology studies were conducted or submitted. The safety is supported by reference to approved combination oral contraceptives containing levonorgestrel and ethinyl estradiol.

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 21-840
- Medical Officer's Review of NDA 21-544
- Medical Officer's Review of IND 63,735
- Consultation reports from other disciplines
- Pubmed searches and journal review

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4.2 Table of Clinical Studies

Table 1 Overview of Clinical Trials

Study	Design	Treatment Groups	Randomized/ Treated*/PITT**	Primary Endpoint
PSE-301 (Primary Study)	Randomized Multicenter Open-label	DP3-84/30: levonorgestrel (150 mcg) and ethinyl estradiol (30 mcg) 84 days combination drug followed by seven days of ethinyl estradiol monotherapy (30 mcg) administered orally for four 91-day cycles.	1025/1013/668	Prevention of Pregnancy (Pearl Index)
		DP3-84/10: (Seasonique) Same combination therapy as DP3-84/30 but followed by seven days of ethinyl estradiol monotherapy (10 mcg) administered orally for four 91-day cycles.	1024/1006/708	

PSE-302 (Supportive Study for PSE-301)	Randomized Multicenter Open-label	<u>DP3-84/30:</u> Administered orally for four 91-day cycles	96/95/67	Co-Primary Endpoints: 1. Safety Evaluation Using Results of Endometrial Biopsy Evaluations 2. Prevention of Pregnancy (Pearl Index)
		<u>DP3-84/10: (Seasonique)</u> Administered orally for four 91-day cycles	95/95/73	
		<u>DP3-25/30:</u> Levonorgestrel (150 mcg) and ethinyl estradiol (30 mcg) 25 days combination drug followed by three days ethinyl estradiol monotherapy (30 mcg), administered orally for thirteen 28-day cycles	94/89/75	
		<u>Nordette:</u> Levonorgestrel (150 mcg) and ethinyl estradiol (30 mcg) 21 days combination drug followed by seven days placebo, administered orally for thirteen 28-day cycles	95/93/76	

* Treated Subjects: those who received at least one dose of study drug, whether or not the subjects ever returned for any post-baseline study visit. This is also referred to as the Safety Cohort.

** PITT Cohort: All treated subjects between 18 and 35 years of age who completed at least one cycle of treatment.

Source: NDA 21-840, Integrated Summary of Efficacy (ISE), Page 13

4.3 Review Strategy

Study PSE-301 and Study PSE-302 were both reviewed in order to evaluate the efficacy and safety of Seasonique. The Applicant is not seeking with this application any claims for DP3-84/30 or DP3-25/30 which were assessed in Study PSE-301 and Study PSE-302, respectively.

Medical Officer's Comment

- *Seasonique is identical to the already approved Seasonale for the first 84 days of each cycle. On Days 85 to 91, Seasonale uses a placebo tablet while Seasonique substitutes seven days of EE 0.01 mg tablets instead of the seven days of placebo. As previously mentioned, questions for this reviewer will be:*
- *Is the product safe and effective as an oral contraceptive?*
- *Does the substitution of EE 0.01 mg for placebo have any added benefit or risk with regard to safety or efficacy?*
- *Should the product be approved if safety and efficacy are similar to that of the already approved Seasonale which has less total ethinyl estradiol?*

- *If the product is safe and effective as an oral contraceptive, should the new formulation be approved because it represents a new approach to oral contraception in spite of the fact that the total estrogen in this formulation may be slightly higher?*

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

4.5 Financial Disclosures

In Study PSE-301, two investigators disclosed financial arrangements with the Applicant.

~~_____~~ (Principal Investigator at Site ~~_____~~ which enrolled ~~_____~~ subjects) received a total of \$36,000.00 in 2001 as compensation for ~~_____~~

~~_____~~ (Principal Investigator at Site ~~_____~~ which enrolled ~~_____~~ subjects) was paid \$30,000.00 by ~~_____~~

In Study PSE-302, two investigators disclosed financial arrangements with the Applicant.

~~_____~~ (Principal Investigator at Site ~~_____~~ which enrolled ~~_____~~ subjects) was ~~_____~~ as noted above.

~~_____~~ (Also a Principal Investigator at Site ~~_____~~), was paid a ~~_____~~ but the amount was not specified.

Medical Reviewer's Comment

- *In correspondence with Barr Pharmaceuticals, Inc., it was disclosed that ~~_____~~ retired on ~~_____~~, and was no longer an investigator in any on-going clinical studies, specifically Study ~~_____~~ (Study ~~_____~~ was initiated in ~~_____~~ and concluded by ~~_____~~*

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

There are no significant review issues with Pharmacokinetics.

5.2 Pharmacodynamics

There are no significant review issues with Pharmacodynamics.

5.3 Exposure-Response Relationships

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

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The claimed indication for Seasonique™ is for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

6.1.1 Methods

Two one year, multicenter, randomized, open-label, clinical studies were performed to evaluate the efficacy of DP3-84/10. PSE-301 was a large, multicenter study of over 2000 subjects designed to assess the efficacy and safety of two 91-day extended regimen doses (DP3-84/30 and DP3-84/10) with over 1000 subjects per treatment group. No regulatory claims are being sought for DP3-84/30. PSE-302 was a smaller, multicenter study designed to obtain baseline and end of treatment endometrial biopsy data on the same two DP3 91-day extended regimen doses used in PSE-301. PSE-302 was conducted as a supportive study to PSE-301. PSE-302 also included two additional exploratory treatment arms: a 28-day DP3 regimen and a 28-day Nordette regimen (approximately 90 subjects in each of the four treatment arms).

6.1.2 General Discussion of Endpoints

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all "On-treatment" pregnancies defined as those pregnancies for which the date of conception was on or after the first date of taking study medication but not more than 14 days after the date of the last dose of combination (LNG/EE) oral contraceptive therapy (i.e. Day 84 for DP3-84/30 and DP3-84/10, Day 25 for DP3-25/30 and Day 21 for Nordette). Any pregnancy that occurred during a partially completed cycle (i.e., before cycle day 84 for DP3-84/10 and DP3-84/30,

before cycle day 25 for DP3-25/30, or before cycle day 21 for Nordette) was included in the Pearl Index calculation and the cycle in which the pregnancy occurred was considered a complete cycle.

For the 91-day extended oral contraceptive (OC) regimen groups (DP3-84/30 and DP3-84/10), the formula for the Pearl Index is:

$$\frac{(100) \times (\text{number of pregnancies}) \times (4 \text{ cycles/year})}{(\text{number of cycles completed})}$$

For the 28-day OC regimen treatment groups (DP3-25/30 and Nordette), the Pearl Index was calculated as:

$$\frac{(100) \times (\text{number of pregnancies}) \times (13 \text{ cycles/year})}{(\text{number of cycles completed})}$$

Two pregnancy rates were calculated to evaluate efficacy:

- The primary efficacy cohort among Pregnancy Intent to Treat (PITT) subjects was all treated subjects between the ages of 18 and 35 years with at least one complete cycle of treatment (84 days of active combination treatment with DP3-84/10) but excluding cycles in which another birth control method was used (“an overall rate”).
- A Pearl Index was also calculated for “compliant use” cycles among PITT subjects. For this calculation, cycles where the subject was deemed to be non-compliant with study drug use were also excluded from the Pearl Index denominator. Non-compliance was defined as: (1) 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% across the study) with study medication (2) Used a prohibited concomitant medication that may interact with OC therapy or (3) Used another form of birth control.

The sample size for the primary Study PSE-301 was primarily a function of the desired extent of exposure to adequately characterize efficacy (i.e. 10,000 women-months) and to adequately characterize safety (a minimum of 200 women per arm who completed one year of treatment). If subjects within a treatment group completed the full one year study (thirteen cycles), then approximately 770 subjects would be adequate to provide an appropriate exposure denominator for the method failure calculation. The sample size of 1020 subjects per treatment arm was chosen to allow for study dropouts and still provide adequate exposure for both efficacy and safety determinations.

Medical Reviewer’s Comment

- *The sample size and duration of treatment is consistent with this Division’s recommendations.*

6.1.3 Study Design

PSE-301 (Primary Clinical Trial)

This primary Phase 3 clinical trial for contraceptive effectiveness and safety is entitled: “A Phase III, Randomized, Multicenter, Clinical Trial to Evaluate the Efficacy and Safety of Combination Oral Contraceptive Regimens Utilizing Ethinyl Estradiol During the Pill-Free Interval for Prevention of Pregnancy in Women”.

The trial utilized multiple investigators across 36 US Centers. The first subject was enrolled on 04/14/02 and the last subject was completed on 04/08/04.

This randomized, multicenter, open-label study had two arms:

- DP3 84/30: LNG 150 mcg and EE 30 mcg in combination for 84 days followed by EE 30 mcg taken for seven days for four 91-day cycles per year. This arm included 1025 randomized subjects of which 1013 were treated. Six hundred sixty-eight subjects completed at least one cycle of treatment (PITT Cohort).
- **DP3-84/10 (Seasonique):** LNG 150 mcg and EE 10 mcg in combination for 84 days followed by EE 10 mcg taken for seven days for four 91-day cycles per year. This arm included 1024 randomized subjects of which 1006 were treated. Seven hundred and eight subjects completed at least one cycle of treatment (PITT Cohort).

The primary objective of this study was to demonstrate the efficacy and safety of the 91-day extended regimen oral contraceptives, DP3-84/10 and DP3-64/30, which include 84 days of combination therapy followed by seven days of ethinyl estradiol monotherapy, taken for one year in women desiring pregnancy prevention.

Secondary objectives included 1) observation of the incidence and severity of hormone-related symptoms during the treatment period and 2) observation of the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) bleeding and/or spotting.

Study Population

The study population consisted of sexually active adult women (ages 18 to 40) of childbearing potential who desired contraception and had no contraindications to the use of oral contraceptives. Subjects were fluent in English and capable of giving informed consent. Expansion of the age range beyond 35 years was done to assess utility of both doses of DP3 in the 36 to 40 year age group.

Medical Reviewer’s Comments

- *The principal cohort for efficacy included only subjects 18-35 years of age who completed at least one cycle on treatment and excluding cycles in which another birth*

control method was used. The final version of the protocol excluded smokers over age of 35 so these subjects were discontinued from the study.

- *The fact that all enrolled subjects were required to be fluent in English could easily lead to an under representation of Hispanic or Asian subjects.*

Inclusion Criteria

- Sexually active adult women (age 18 through 40 at initiation of study drug) who were at risk for pregnancy who:
- Had a history of oral contraceptive (OC) use prior to enrollment (Continuous Users) or
- Had no history of prior OC use (Fresh Starts) or
- Had a history of OC use, but not within the six months prior to enrollment (Prior Users)
- Had a negative pregnancy test
- Signed informed consent
- Agreed to use OC therapy as their primary birth control method

Medical Reviewer's Comment

- *The inclusion criteria are acceptable.*

Exclusion Criteria

- History of hypersensitivity to estrogen or progestin component of OCs
- History of alcohol or drug abuse which, in the opinion of the investigator, makes the patient unfit for participation in the study
- Active smoker older than 35 years of age at initiation of study drug
- 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-PÉG, Grisactin, Ultragris), ampicillin, (e.g., Omnipen, Principen, Totalcillin, Unasyn), tetracyclines (e.g., Achromycin, Aureomycin, Cyclopar, Declomycin, Dynacin, Minocin, Panmycin, Retet, Sumycin, Tetrachel, Terramycin, Vectrin, Vibramycin, Vibra-Tabs), or any generic equivalents
- History of being HIV or Hepatitis C positive
- History of persistent noncompliance with any chronic medication
- History of having received injectable hormone therapy (e.g., Depo-Provera) within the 10 months prior to study enrollment or having a progestin-releasing intrauterine device (IUD) in place within one month prior to initiation of study drug or having had a contraceptive implant removed within one month prior to initiation of study drug or has received any other form of hormonal contraception within 3 months prior to initiation of study drug except oral contraceptives
- Routine concomitant use of forms of contraception (IUD, diaphragm, contraceptive sponge, condoms) unless prudent for situations specified in the protocol

- Patients who have had recent surgical or medical abortion, miscarriage, or vaginal or cesarean delivery must have had at least three consecutive, normal menstrual cycles prior to initiation of study drug
- Undiagnosed abnormal genital bleeding
- History of thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease
- History of uncontrolled or untreated hypertension (systolic BP $\geq$ 140 mm Hg or diastolic BP $\geq$ 90 mm Hg)
- Known or suspected carcinoma of the breast, endometrial carcinoma, or known or suspected estrogen-dependent neoplasia
- History of hepatic adenomas or carcinomas
- History of cholestatic jaundice of pregnancy, or jaundice with prior OC use
- Known or suspected pregnancy or currently breast feeding
- Hyperlipidemia requiring active treatments with hyperlipidemic agents
- Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam, or any laboratory finding that contraindicates the use of OCs
- Had participated in any clinical investigation utilizing investigation drugs or medical devices within 30 days prior to enrollment
- Had donated or sustained a loss of more than 500 mL of blood within 30 days prior to initiation of study drug

Medical Reviewer's Comment

- *The exclusion criteria are acceptable. It is important to note that as a preventative to sexually transmitted diseases, condom use was permitted. However, these cycles were excluded in the PITT efficacy analysis.*

Removal of Subjects from Therapy or Assessment

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

- Subject missed three or more pills in a row
- 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 lost to follow-up
- Subject refused to cooperate with the required study procedures
- Subject older than 35 years of age who began smoking while on study medication
- Subject who had a clinic visit following the final week of a cycle that resulted in a lapse of study medication intake (i.e., the subject returned for a clinic visit beyond Day 91 of a cycle).

Treatment Arms

A total of 2049 subjects were randomized using an Interactive Voice Response System (IVRS) in a 1:1 fashion to one of two treatment arms:

- DP3-84/30: LNG 150 mcg/EE 30 mcg for 84 days followed by seven days of EE (30 mcg) monotherapy; orally for four 91-day cycles, (N=1025 randomized, N=1013 treated)
- **DP3-84/10 (Seasonique):** LNG 150 mcg/EE 30 mcg for 84 days followed by seven days of EE (10 mcg) monotherapy; orally for four 91-day cycles, (N=1024 randomized, N=1006 treated)

Among those randomized, a total of 2019 actually took at least one dose of study medication. A total of 1567 of the 2019 (77.6%) of subjects who started treatment completed at least one cycle of study medication. Of these, a total of 1376 of the 1567 (87.8%) subjects who completed at least one cycle of study medication were between 18 and 35 years of age. Thirty subjects, who were randomized to treatment, discontinued the study prior to taking their first dose of study medication: 11 became pregnant prior to initiating study drug, three subjects withdrew their consent, one was lost to follow-up, one experienced an adverse event (AE) that led her to be discontinued from the study, one had abnormal lab values that excluded her from participating in the study, and 13 never started study medication for other reasons (other choices of birth control methods, irregular menstrual cycles prior to initiation of study medication, etc.)

Duramed Research, Inc. supplied all study drugs. The treatment group was not revealed to the subject prior to signing the informed consent form. Once randomized, each subject was managed in an open-label fashion. All subjects, regardless of treatment group were to initiate therapy on the first Sunday following the beginning of their menstrual period (“Sunday starters”) and were to remain Sunday starters throughout the study.

Study Procedures

A Screening Visit took place for all potential subjects 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), clinical laboratory tests (CBC, serum chemistry, lipid profile, and 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 (Baseline) took place within four weeks after the Screening Visit during the final week of the menstrual cycle prior to beginning study therapy and after all results of tests done at screening were known. During this visit, subjects were randomized via Interactive Voice Response System (IVRS) to one of the two treatment arms. Open-label study medication and an electronic diary were dispensed and training was provided to the subject for recording study

compliance, hormonal symptoms, and bleeding and/or spotting information. If the screening evaluation was completed more than two weeks prior to the initiation of study therapy, the urine pregnancy test was repeated at Visit 1.

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. Following Visit 1, subjects were contacted by phone the Monday following the anticipated study medication start date, to document that the menstrual period and study medication had started as anticipated and to schedule the day of Visit 2. All subjects received a 13-week supply of study drug at Visit 1 and at each subsequent clinic visit at Weeks 13, 26, and 39. All visits were to have taken place within seven days prior to completion of study medication for that cycle. The end-of-study evaluation took place approximately two weeks following the last cycle of study OC therapy, following completion of withdrawal menses. Any subject who withdrew or who was withdrawn from the study was to have end-of-study evaluations completed in the same manner as those who completed the full term of study participation.

All subjects were followed for three months following completion of the study or early withdrawal for the occurrence of pregnancy. Subjects who became pregnant during the course of the study were followed via clinic visits after study completion until eight weeks following delivery or termination of pregnancy. Infants were to be followed for eight weeks following delivery via a written report from a family physician, obstetrician, or pediatrician.

The study schedule of procedures is illustrated in Table 2.

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Table 2 Study Schedule

Parameter	Screening	Visit 1	Visit 2-4 ^a	Phone Call ^{d,g}	Completion of Therapy ^c	Post Study Follow-up ^f
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				X	
Randomization		X				
Clinical laboratory tests ^b	X				X	
Urine pregnancy test	X	X	X	X ^{e,h}	X	X
Urine pregnancy test kits distribution		X	X	X	X	
Study drug distribution		X	X			
Electronic diary distribution						
Study drug compliance			X	X	X	
Adverse event recording			X	X	X	
Concomitant medications	X	X	X	X		
Change in smoking history		X	X	X	X	

^a Subjects seen at Weeks 13, 26 and 39

^b CBC, serum chemistry, urinalysis, fasting lipid profile

^c Approximately 14 days after completion of fourth cycle of therapy

^d Monthly except the month of the scheduled clinic visit

^e Subjects were instructed to perform a urine pregnancy test prior to the scheduled monthly phone call if two consecutive pills were missed during the previous month.

^f After study completion/withdrawal, subjects were followed via a monthly phone call for occurrence of pregnancy or until the menstrual cycle was determined to return to normal for the subject.

^g Subjects were contacted by phone on the Monday following the anticipated Sunday start day.

^h Subjects were instructed to perform a urine pregnancy test at home if the menstrual period was delayed.

Source: NDA 21-840, Clinical Study Report, PSE-301, Page 28

Primary Efficacy Assessment

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all “On-treatment” 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 (Day 84 for DP3-84/30 and 84/10, Day 25 for DP3-25/30 and Day 21 for Nordette).

Pregnancy rates were calculated based on the following considerations:

- Pregnancy was defined by a positive pregnancy test.
- Conception date was based on the ultrasound information when available.
- If the date of conception clearly occurred before the date of first dose of study medication, then the pregnancy was not considered to be an “On-treatment” pregnancy.

- If the date of conception clearly occurred more than 14 days after the date of last dose of combination study medication, then the pregnancy was not considered to be an “On-treatment” pregnancy.
- If no ultrasound-based estimate of conception date was available, or the pregnancy status of a woman was unknown (e.g., delivery date was unknown because the subject was lost to follow-up), then the pregnancy was counted as an “On-treatment” pregnancy. Otherwise, the pregnancy was further evaluated to determine if it was an on-treatment or off-treatment pregnancy.

Two primary cohorts were analyzed:

The Intent to Treat (ITT) cohort consisted of subjects who were randomized to treatment and completed at least one cycle of study medication. The ITT served as the principal subject cohort for all endpoints other than pregnancy. A “complete cycle” was defined as one where the subject completed all 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 Pregnancy Intent to Treat (PITT) cohort consisted of subjects in the ITT cohort between 18 and 35 at initiation of therapy. For this cohort, the cycle in which a subject became pregnant was also considered a complete cycle. Efficacy, expressed as the Pearl Index, was evaluated from the “On Treatment” pregnancy rate in the PITT cohort (excluding cycles in which another birth control method was used).

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 would not be included in the Intent to Treat (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.

The Safety Cohort (discussed later in this review) consisted of all subjects who received at least one dose of study medication. Subjects for whom dose verification could not be established were included, with the assumption that they took at least one dose of study medication.

Within the ITT and PITT cohorts, subsets of subjects were created based on body weight and “compliant use” with oral contraceptives. Subjects with body weight at baseline < 90 kg (ITT and PITT) and ≥ 90 kg (ITT) were evaluated. In addition, subject cycles that were deemed non-compliant (defined as all cycles in which a subject skipped two or more consecutive pills or had a pattern of substantial non-compliance with study medication, or used a protocol prohibited concomitant medication that may interact with OC therapy) were not used. Substantial non-compliance was defined as an overall pill compliance of less than 80%.

Medical Reviewer’s Comment

- *The criteria for “On-treatment” pregnancy are acceptable. If a conception date could not be adequately determined, the pregnancy was considered to be “On-treatment”.*

The “On-treatment” pregnancy rate was calculated using the Pearl Index and life table analyses. The denominators of the pregnancy rates presented in the efficacy analysis are as follows:

- The “Typical-Use” Pregnancy Rate: All complete cycles for subjects in the PITT cohort (subjects 18-35 years of age at the Screening Visit) in which no other birth control method 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 and the subject was deemed to be compliant during the cycle.
- The “All Users” Pregnancy Rate: All subjects with at least one complete cycle on study medication, as defined by the ITT cohort.

Medical Reviewer’s Comment

- *The primary efficacy endpoint was the pregnancy rate as calculated by the Pearl Index in the “Typical-Use” PITT cohort in which no other birth control method was used.*

Pregnancy Testing/Assessment

All urine pregnancy tests were performed using the ~~_____~~ Pregnancy test kit. Urine pregnancy tests were conducted at the Screening Visit, at randomization (Visit 1), every clinic visit (Weeks 13, 26, and 39), and at the completion of therapy or upon early withdrawal from the study. All subjects were followed for three months following completion of the study or early withdrawal for the occurrence of pregnancy.

Demographics

The demographics are presented in the following two tables. Table 3 represents the entire ITT population. Table 4 focuses on the 18-35 age group on which the primary efficacy analysis is based.

Table 3 Demographic Information at Screening, ITT Population (Subjects with at Least One Complete Cycle on Treatment), Study PSE-301

	DP3-84/30 (N=768)	DP3-84/10 (N=799)	Total (N=1567)
Mean Age (yrs)	27.6	27.5	27.6
Mean Weight (lbs)	153.9	155.6	154.8
Race			
African-American	71 (9.2%)	87 (10.9%)	158 (10.1%)
Asian	19 (2.5%)	17 (2.1%)	36 (2.3%)

Caucasian	630 (82.0%)	641 (80.2%)	1271 (81.1%)
Hispanic	40 (5.2%)	37 (4.6%)	77 (4.9%)
Other	8 (1.0%)	17 (2.1%)	25 (1.6%)
Smoking Status			
Non-Smoker	582 (75.8%)	652 (81.6%)	1234 (78.7%)
Smoker	186 (24.2%)	147 (18.4%)	333 (21.3%)
Prior OC Usage			
Continuous User ¹	520 (67.7%)	548 (68.6%)	1068 (68.2%)
Prior User ²	182 (23.7%)	175 (21.9%)	357 (22.8%)
Fresh Start ³	66 (8.6%)	76 (9.5%)	142 (9.1%)

¹ Had history of OC use prior to enrollment

² Had history of OC use, but not within six months prior to enrollment

³ Had no prior history of OC use

Source: NDA 21-840, Clinical Study Report, Page 60

Medical Reviewer's Comment

- *The fact that all enrolled subjects were required to be fluent in English could account for the small percentages of Asian and Hispanic study subjects.*

Table 4 Demographic Information at Screening, PITT Population (Subjects 18-35 Years of Age with at Least One Complete Cycle on Treatment), Study PSE-301

	DP3-84/30 (N=668)	DP3-84/10 (N=708)	Total (N=1376)
Mean Age (yrs)	26.1	26.2	26.1
Mean Weight (lbs)	154.6	154.9	154.8
Race			
African-American	64 (9.6%)	80 (11.3%)	144 (10.5%)
Asian	16 (2.4%)	16 (2.3%)	32 (2.3%)
Caucasian	545 (81.6%)	562 (79.4%)	1107 (80.5%)
Hispanic	36 (5.4%)	34 (4.8%)	70 (5.1%)
Other	7 (1.0%)	16 (2.3%)	23 (1.7%)
Smoking Status			
Non-Smoker	489 (73.2%)	570 (80.5%)	1059 (77.0%)
Smoker	179 (26.8%)	138 (19.5%)	317 (23.0%)
Prior OC Usage			
Continuous User ¹	448 (67.1%)	484 (68.4%)	932 (67.7%)
Prior User ²	159 (23.8%)	152 (21.5%)	311 (22.6%)
Fresh Start ³	61 (9.1%)	72 (10.2%)	133 (9.7%)

¹ Had history of OC use prior to enrollment

² Had history of OC use, but not within six months prior to enrollment

³ Had no prior history of OC use

Source: NDA 21-840, Clinical Study Report, Page 62

Medical Reviewer's Comments

- Review of NDA 21-544 (Seasonale) showed that 77.0% of subjects in that study were Caucasian, 10.9% African-American, 2.2% Asian, and 7.0% Hispanic .
- The demographic data shows that the treatment arms appear similar. It is noted in both of the prior two tables that the number of fresh starts was quite low compared to prior and continuous users. This tends to bias the study population to those women who have had fewer problems with OCs and/or are more tolerant of side effects. A study population of entirely fresh starts may have had more discontinuations for unanticipated bleeding than was demonstrated in this study.

Subject Disposition

A total of 2049 subjects were randomized and 2019 were treated as follows:

- DP3-84/30: 1025 subjects were randomized and 1013 subjects were treated.
- **DP3-84/10**: 1024 subjects were randomized and 1006 subjects were treated.

Table 5 summarizes the number of randomized subjects by treatment group included in each of the subject cohorts.

Table 5 Subject Cohorts, Study PSE-301

	DP3-84/30 (N=1025)		DP3-84/10 (N=1024)		Total (N=2049)	
	N	%	N	%	N	%
Randomized	1025	100	1024	100	2049	100
Treated Subjects (Safety)	1013	98.8	1006	98.2	2019	98.5
Treated at Least One Complete Cycle (ITT)	768	74.9	799	78.0	1567	76.5
< 90 kg	671	65.5	694	67.8	1365	66.6
≥ 90 kg	97	9.5	105	10.3	202	9.9
ITT 18-35 Years of Age (PITT)	668	65.2	708	69.1	1376	67.2
< 90 kg	581	56.7	616	60.2	1197	58.4

Source: NDA 21-840, Clinical Study Report, Page 51

Bleeding and/or spotting episodes were cited as the reason for study discontinuation both through adverse events and subject decision to withdraw. In the DP3-84/30 group, 85 of the 200 (42.5%) AEs that led to study discontinuation were related to bleeding and/or spotting. In the DP3-84/10 group, 62 of the 164 (37.8%) AEs were related to bleeding and/or spotting. Bleeding and/or spotting was cited as at least part of the subject's decision to withdraw in 20 of the 130 subjects in the DP3-84/10 group (15.4%) who withdrew their consent (See Table 6).

Table 6 Disposition of All Treated Subjects (Safety), Study PSE-301

	DP3-84/30 (N=1013)		DP3-84/10 (N=1006)		Total (N=2019)	
	N	%	N	%	N	%
Safety Cohort	1013	100	1006	100	2019	100
Discontinued Study	534	52.7	506	50.3	1040	51.5
Primary Reason for Discontinuation						
Adverse Event	200	19.7	164	16.3	364	18.0
Subject Decision	113	11.2	130	12.9	243	12.0
Non-Compliance with Study Protocol	36	3.6	38	3.8	74	3.7
Lost to Follow-Up	149	14.7	149	14.8	298	14.8
Pregnancy	18	1.8	5	0.5	23	1.1
Investigator's Discretion	1	0.1	2	0.2	3	0.1
Other/Unknown	17	1.7	18	1.8	35	1.7

Source: NDA 21-840, Clinical Study Report, Page 52

Medical Reviewer's Comments

- *As mentioned above, of the 164 subjects in the DP3-84/10 arm who withdrew from the study due to an adverse event, 62 of these withdrawals were related to bleeding and/or spotting (37.8%).*
- *Twenty of the 130 subjects in the "Subject Decision" group cited bleeding and/or spotting as contributing to the decision to withdrawal.*
- *Two Hundred Ninety-Four (294) of the total 506 discontinuations were bleeding and/or spotting related (58.1%).*
- *Discontinuation rates were similar in all study arms and most were due to adverse events. Unfortunately, since Seasonale was not used as a comparator, we cannot assess discontinuation rates relative to the already approved extended cycle product. However, in NDA 21-544, the Seasonale overall discontinuation rate was 40.6%.*

Primary Efficacy Assessments and Endpoints

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

Table 7 Pearl Index Calculation of Treatment Failure Rates in Subjects 18-35 years of Age With at Least One Complete Cycle of Treatment (PITT) and Excluding Cycles in Which Another Birth Control Method Was Used, Study PSE-301

Treatment Group	Number of Cycles	Number of 28-Day Patient Months	Number of "On-Drug" Pregnancies	Pearl Index
DP3-84/30	1461	4748.25	10	2.74
DP3-84/10 (Seasonique)	1577	5125.25	5	1.27

Source: NDA 21-840, Clinical Study Report, Page 71

Medical Reviewer's Comments

- *The total number of completed 28-day patient-months studied in the DP3-84/30 arm was 6669.00. However, 1920.75 patient-months were excluded from the Pearl Index calculation because another birth control method was used so the calculation was based on 4748.25 patient-months.*
- *The total number of completed 28-day patient-months studied in the DP3-84/10 (Seasonique) arm was 7075.25. However, 1950.00 patient-months were excluded from the Pearl Index calculation because another birth control method was used so the calculation was based on 5125.25 patient-months.*
- *The total number of patient-months studied in PSE-301 for DP3-84/30 and DP3-84/10 was 9873.50 which is close to the 10,000 patient-months recommended by the Division.*
- *The total number of patient-months studied (excluding cycles in which another birth control method was used) for DP3-84/10 in Study PSE-301 was 5125.25. In the primary efficacy study for NDA 21-544 (Seasonale) 5946 patient-months (excluding cycles in which another birth control method was used) were studied. There is no theoretical reason to assume that Seasonique should have a lower Pearl Index than Seasonale so that 5125.25 28-day patient-months is acceptable and adequate for calculating a Pearl Index.*
- *The Applicant's Pearl Index of 1.27 is based on five "On-treatment" pregnancies. When pregnancies in this study were reviewed, the medical officer believed that it was possible that two additional "On-treatment" pregnancies could have occurred thus giving a total of seven "On-treatment" pregnancies. The Pearl Index for Seasonique was then recalculated by the FDA statistician to be 1.77 (95% CI 0.71, 3.64) which is acceptable in light of other contraceptive approvals that have allowed rates of up to 2.39.*
- *The original NDA for Seasonal (NDA 21-544) reported four "On-treatment" pregnancies in 811 completed 91 day cycles resulting in a Pearl Index of 1.97 per 100 women-years of use. The FDA statistician used 809 completed cycles in the Pearl Index calculation resulting in a rate of 1.98 (0.54, 5.03). Approved OCs also studied in NDA 21-544 were Nordette (Pearl Index 2.22), and Levlite (Pearl Index 3.75).*

Efficacy Conclusions

In this study, the 91-day extended regimen combination oral contraceptive, DP3-84/10 (Seasonique), was given for one year in women ages 18-35 desiring pregnancy prevention. When no other method of contraception was used, the Pearl Index, as calculated by the Applicant in this cohort was 1.27 per 100 women-years of use.

Medical Reviewer's Comments

- *Although a minimum of 10,000 28-day cycles is usually studied for new oral contraceptives, this is an approved contraceptive formulation dose (approved since 1982)*

that only differs in the dosing duration and the addition of the 0.01 mg of EE monotherapy. The 5125.25 patient-months is therefore considered sufficient for efficacy.

- *The Pearl Index for Seasonique as calculated by the FDA statistician (based on seven "On-treatment" pregnancies instead of five) was determined to be 1.77 (95% CI 0.71,3.64).*
- *The Applicant has clearly demonstrated the contraceptive efficacy of Seasonique.*
- *No attempt was made in this NDA to show the benefit of substituting the EE 0.01 mg monotherapy for placebo.*

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Pregnancy Case Listings for Seasonique Treated Subjects

Table 8 Reported Pregnancies in the in the Seasonique Treatment Group, Study PSE-301

Site/ Pt #	Age/ Wt. in lbs.	User Type	Drug Start Date	Drug Stop Date	Date of Positive Preg Test	Conception Date	Applicant Considers Preg On/Off Treatment*	MO Considers Preg On/Off Treatment	MO Evaluation of Compliance
1/228	21/137	C	09/22/02	06/13/03	09/08/03	08/26/03 By LMP	Off	Off	N/A
1/251	30/138	C	10/13/02	01/12/03	None	02/24/03 By LMP	Off	Off	N/A
1/254	28/152	C	10/20/02	11/14/02	01/30/03	01/10/03 By Ultrasound	Off	Off	N/A
13/2603	22/190	C	05/05/02	11/02/02	02/04/03	11/19/02 By Ultrasound	Off	Off	N/A
13/2611	24/154	C	05/19/02	08/10/02	10/08/02	08/21/02 By Ultrasound	On	On	Non-Compliant
14/2802	24/110	C	04/28/02	04/26/03	05/29/03	05/06/03 By Ultrasound	Off	Off	N/A
14/2822	34/141	C	05/19/02	10/06/02	11/13/02	10/23/02 By Ultrasound	Off	Off	N/A
17/3408	29/118	C	07/07/02	01/04/03	03/31/03	02/20/03 By Ultrasound	Off	Off	N/A
19/3831	25/134	P	09/22/02	01/16/03	01/16/03	12/15/02 By Ultrasound	Off	On	Non-Compliant
20/4019	27/153	C	05/26/02	05/24/03	06/30/03	06/12/03 By Ultrasound	Off	Off	N/A
20/4092	36/172	C	02/02/03	02/15/03	03/21/03	03/04/03 By Ultrasound	Off	Off	N/A
21/4205	20/194	P	05/05/02	06/16/02	None	07/09/02 By Ultrasound	Off	Off	Non-Compliant
25/5021	25/124	P	06/09/02	06/07/03	06/30/03	05/22/03 By Ultrasound	On	On	N/A
25/5039	26/144	P	08/04/02	04/22/03	04/24/03	04/15/03 By Ultrasound	On	On	N/A
29/5830	23/165	F	07/07/02	07/05/03	None	07/11/03 By Ultrasound	On	On	N/A
29/5886	21/137	P	12/22/02	01/06/03	02/25/03	01/27/03 By Ultrasound	Off	Off	N/A
30/6018	23/139	C	06/16/02	06/14/03	None	07/08/03 By Ultrasound	Off	Off	N/A
36/7238	30/126	P	10/27/02	10/24/03	12/12/03	10/31/03 By Ultrasound	On	On	N/A
32/6450	19/183	F	12/01/02	Unsure	None	Unverified	Off	On	Non-Compliant

* First day of study drug use to 14 days following last dose date

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 21-840, Clinical Study Report, Adapted from Page 96 and the narrative summaries

Subject 19/3831 began taking study medication on 9/22/02. She had a negative urine pregnancy test on 12/20/02 (Visit 2). She reported that her last menstrual period began on 12/18/02. On _____, she was seen the emergency room because of vomiting. Serum beta HCG was positive

(12,604 mIU/mL). On 1/16/03, ultrasound was performed which revealed a viable intrauterine pregnancy of six weeks, four days gestation. The estimated date of conception based on the ultrasound was 12/15/02. This subject was non-compliant so that drug accountability could not be done however this reviewer disagrees with the Applicant and considers this to be an “On-treatment” pregnancy.

Subject 32/6450 was randomized and began taking study drug on 12/01/02. She failed to return for Visit 2 and the Site was unable to contact her. On 03/31/03, the subject called the Site and reported that she had a positive urine pregnancy test. She stated that her last dose of study drug was “around” 03/15/03 and that she had been non-compliant and skipped doses. Drug accountability placed the last dose on 02/27/03. The date of last dose by electronic diary was 12/23/02. When she reported the pregnancy on 03/31/03, she also informed the Site that she did not want to have a pregnancy test or ultrasound and that her last menstrual period was “around the end of February”. She also declined all final study procedures and stated that she planned to terminate the pregnancy. The Applicant considers this to be an “Off-treatment” pregnancy because the history is vague and the pregnancy is unverified but this reviewer considers this pregnancy to be “On-treatment”.

Medical Reviewer’s Comment

- *It is not unreasonable to consider the above two pregnancies as occurring “On-treatment” thus increasing total “On-treatment” pregnancies to seven.*

PSE-302 (Supportive Study for PSE-301)

This supportive Phase 3 clinical trial for contraceptive effectiveness and safety is entitled: “A Phase III, Randomized, Multicenter, Clinical Trial to Evaluate the Efficacy For Prevention of Pregnancy in Women and Safety by Obtaining Endometrial Biopsies of Combination Oral Contraceptive Regimens Utilizing Ethinyl Estradiol During the Pill-Free Interval”.

The trial utilized multiple investigators across seven US Centers. The first subject was enrolled 04/28/02 and the last subject was completed on 04/13/04.

This randomized, multicenter, open-label study had four arms:

- DP3 84/30: LNG 150 mcg and EE 30 mcg in combination for 84 days followed by EE 30 mcg taken for seven days for one year (four 91-day cycles). This arm included 96 randomized subjects of which 95 were treated. Sixty-seven subjects completed at least one cycle of treatment (PITT Cohort).
- **DP3-84/10 (Seasonique):** LNG 150 mcg and EE 30 mcg in combination for 84 days followed by EE 10 mcg taken for seven days for one year (four 91-day cycles). This arm included 95 randomized subjects of which 95 were treated. Seventy three subjects completed at least one cycle of treatment (PITT Cohort).
- DP3-25/30: LNG 150 mcg and EE 30 mcg in combination for 25 days followed EE 30 mcg monotherapy taken for three days; administered orally for thirteen 28 day cycles.

This arm included 94 randomized subjects of which 89 were treated. Seventy five subjects completed at least one cycle of treatment (PITT Cohort).

- Nordette® -28 (Wyeth-Ayerst Laboratories, Philadelphia, PA): LNG 150 mcg and EE 30 mcg in combination for 21 days followed by seven days placebo tablets; administered orally for thirteen 28 day cycles. This arm included 95 randomized subjects of which 93 were treated. Seventy six subjects completed at least one cycle of treatment (PITT Cohort).

This study had two primary objectives. The first primary objective was to demonstrate the efficacy and safety of the 91-day extended combination oral contraceptive regimens, DP3-84/10 and DP3-84/30 taken for one year in women desiring pregnancy prevention and the second primary objective was to evaluate endometrial biopsies done before and at the end of the study.

Secondary objectives included 1) observation of the incidence and severity of hormone-related symptoms during the treatment period and 2) observation of the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) bleeding and/or spotting.

Medical Reviewer's Comment

- *The endometrial biopsy data and the bleeding data will be discussed in the Safety section of this review.*

Study Population

The study population consisted of sexually active women, age 18 to 40 years inclusive, who were at risk for pregnancy. Volunteers were required to be fluent in English and capable of giving informed consent, to agree to use the study oral contraceptive therapy as their primary birth control method and to undergo endometrial biopsy prior to and at the end of the study. Expansion of the age range beyond 35 years was done to assess utility of the three DP3 doses in the 36-40 year age group. Several smokers > 35 years of age were enrolled as permitted under Versions 1 and 2 of the protocol. With the approval of protocol Version 3 that excluded smokers > 35 years of age, these subjects were discontinued.

Medical Reviewer's Comment

- *The fact that all enrolled subjects were required to be fluent in English could easily lead to an under representation of Hispanic or Asian subjects.*

Inclusion Criteria

The inclusion criteria were identical to those in Study PSE-301. The only additional inclusion criterion was that subjects had to agree to undergo endometrial biopsies at the beginning and end of the study.

Exclusion Criteria

These were identical to those in Study PSE-301.

Medical Reviewer's Comment

- *The exclusion criteria are acceptable. It is important to note that as a preventative to sexually transmitted diseases, condom use was permitted.*

Removal of Subjects from Therapy or Assessment

- Subject missed three or more pills in a row
- 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 lost to follow-up
- Subject refused to cooperate with the required study procedures
- Subject older than 35 years of age who began smoking while on study medication
- Subject who had a clinic visit following the final week of a cycle that resulted in a lapse of study medication intake (i.e., the subject returned for a clinic visit beyond Day 91 of a DP3-84/30 or DP3-84/10 cycle, or beyond Day 28 of a DP3-25/30 or Nordette cycle).

Treatment Arms

A total of 380 subjects were randomized using an Interactive Voice Response System (IVRS) in a 1:1:1:1 fashion to one of four treatment arms:

- DP3-84/30: N=96 randomized, N = 95 treated
- **DP3-84/10 (Seasonique):** N=95 randomized, N = 95 treated
- DP3-25/30: N=94 randomized, N = 89 treated
- Nordette®-28: N=95 randomized, N = 93 treated

Among those randomized, a total of 372 actually took at least one dose of study medication. A total of 325 of the 372 (87.4%) subjects who started treatment completed at least one cycle of treatment: 73 (76.8%) of the 95 treated with DP3-84/30, 80 (84.2%) of the 95 treated with DP3-84/10, 84 (94.4%) of the 89 treated with the DP3-25/30 28-day regimen, and 88 (94.6%) of the 93 treated with the Nordette 28-day regimen. A total of 291 subjects of the 372 treated (78.2%) who completed at least one cycle of treatment were between 18 and 35 years of age. Eight patients who were randomized to treatment discontinued the study prior to taking their first dose of study medication: Three were lost to follow-up, one said that she would not have time to participate, one reported that her spouse had been vasectomized, one was reported as no longer being at risk for pregnancy, one who was on Nexium did not wish to take it and study drug at the same time, and one refused to have her baseline biopsy repeated after the first attempt yielded insufficient tissue for analysis.

Duramed Research, Inc. supplied all study drugs. The treatment group was not revealed to the subject prior to signing the informed consent form. Once randomized, each subject was managed in an open-label fashion. All subjects, regardless of treatment group, were to initiate therapy on the first Sunday following the beginning of their menstrual period (“Sunday starters”) and were to remain Sunday starters throughout the study.

Study Procedures

A Screening Visit took place for all potential subjects 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), clinical laboratory tests (CBC, serum chemistry, lipid profile, and 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 (Baseline) took place within four weeks after the Screening Visit during the final week of the menstrual cycle prior to beginning study therapy and after all results of tests done at screening were known. During this visit, an endometrial biopsy was performed and a urine pregnancy test was re-administered for all women. Also during this visit, subjects were randomized via Interactive Voice Response System (IVRS) to one of the four treatment arms. Open-label study medication and an electronic diary were dispensed and training was provided to the subject for recording study compliance, hormonal symptoms, and bleeding and/or spotting information. Paper diaries were not used in this study.

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. Following Visit 1, subjects were contacted by phone the Monday following the anticipated Sunday medication start date, to document that menstrual period and study medication had started as anticipated and to schedule Visit 2.

There were no dosage adjustments, other than in the event that pills were missed, as outlined in the protocol.

Subjects randomized to DP3-84/30 or DP3-84/10 received a 13-week supply (one 91-day cycle) of study drug at the randomization visit and at each subsequent clinic visit during Weeks 13, 26, and 39. Subjects randomized to DP3-25/30 or Nordette received a 12-week supply (three 28-day cycle packs) of study drug at the randomization visit and at subsequent clinic visits during Weeks 12 and 24. During the clinic visit at Week 36, subjects randomized to DP3-25/30 or Nordette received a 16-week supply (four 28-day cycle packs) of study medication.

All visits were to have taken place within seven days prior to completion of study medication for that cycle. The end-of-study evaluation took place approximately two weeks following the last

cycle of study OC therapy, following completion of withdrawal menses. Any subject who withdrew or who was withdrawn from the study was to have end-of-study evaluations completed in the same manner as those who completed the full term of study participation.

All subjects were to be followed for three months following completion of the study or early withdrawal for the occurrence of pregnancy. Subjects who became pregnant during the course of the study were followed for eight weeks following delivery or termination of the pregnancy. Infants were also followed for eight weeks following delivery.

The study schedule of procedures is given in Table 9.

Table 9 Study Schedule

Parameter	Screening	Visit 1	Visit 2-4 ^a	Phone Call ^e	Completion of Therapy ^c	Post Study Follow-up ^g
Informed consent	X					
Medical and contraceptive history	X					
Physical exam including pelvic exam	X				X	
Weight, vital signs	X	X	X		X	
Pap smear	X				X	
Endometrial Biopsy ^d		X				
Randomization		X				
Clinical laboratory tests ^b	X				X	
Urine pregnancy test	X	X	X	X ^h	X	
Urine pregnancy test kits distribution		X	X		X	X
Study drug distribution		X	X			
Electronic diary distribution		X				
Study drug compliance			X	X	X	
Adverse event recording			X	X	X	
Concomitant medications	X	X	X	X		
Change in smoking history		X	X	X	X	

^a Subjects randomized to DP3-84/30 or DP3-84/10 were seen at Weeks 13, 26, and 39. Subjects randomized to DP3-25/30 or Nordette were at Weeks 12, 24, and 40.

^b CBC, serum chemistry, urinalysis, fasting lipid profile

^c Completion of therapy took place approximately 14-days after the last day of study drug.

^d Subjects randomized to DP3-84/30 and -84/10 were divided into two groups. Group 1 underwent end of study biopsy between days 60-84 of the last treatment cycle. Group 2 underwent end of study biopsy between days 89-91 of the last treatment cycle. Subjects randomized to DP3-25/30 underwent end of study biopsy between days 26-28 and Nordette subjects underwent biopsy between days 11-21 of the last treatment cycle.

^e Subjects were contacted by phone monthly regarding adverse events, change in smoking history, concomitant medications, and compliance.

^f Subjects were instructed to perform a pregnancy test prior to the scheduled monthly phone call if two consecutive pills were missed during the previous month.

^g After study completion/withdrawal, subjects were followed via a monthly phone call for the occurrence of pregnancy and until the menstrual cycle was determined to return to normal.

^h Subjects were instructed to perform a urine pregnancy test at home if the menstrual period did not start as anticipated.

Source: NDA 21-840, Clinical Study Report, PSE-302, Page 31

Primary Efficacy Assessment

Efficacy was evaluated from the overall pregnancy rate, calculated by the Pearl Index using all “On-treatment” 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 (Day 84 for DP3-84/30 and 84/10, Day 25 for DP3-25/30 and Day 21 for Nordette).

Pregnancy rates were calculated based on the following considerations:

- Pregnancy was defined by a positive pregnancy test.
- Conception date was based on the ultrasound information when available.
- If the date of conception clearly occurred before the date of first dose of study medication, then the pregnancy was not considered to be an “On-treatment” pregnancy.
- If the date of conception clearly occurred more than 14 days after the date of last dose of combination study medication, then the pregnancy was not considered to be an “On-treatment” pregnancy.
- If no ultrasound-based estimate of conception date was available, or the pregnancy status of a woman was unknown (e.g., delivery date was unknown because the subject was lost to follow-up), then the pregnancy was counted as an “On-treatment” pregnancy. Otherwise, the pregnancy was further evaluated to determine if it was an on-treatment or off-treatment pregnancy.

Two primary cohorts were analyzed:

The Intent to Treat (ITT) cohort consisted of subjects who were randomized to treatment and completed at least one cycle of study medication. The ITT served as the principal subject cohort for all endpoints other than pregnancy. A “complete cycle” was defined as one where subjects randomized to DP3-84/30 or DP3-84/10 completed all 84 days of combination tablets. For DP3-25/30, a “complete” cycle was defined as one where all 25 days of combination pill dosing had taken place, and for Nordette, a “complete” cycle was defined as one where all 21 days of combination pill dosing had taken place. 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 Pregnancy Intent to Treat (PITT) cohort consisted of subjects in the ITT cohort between 18 and 35 at initiation of therapy. For this cohort, the cycle in which a subject became pregnant was also considered a complete cycle. Efficacy, expressed as the Pearl Index, was evaluated from the “On-treatment” pregnancy rate in the PITT cohort (excluding cycles in which another birth control method was used).

The Safety cohort (discussed later in this review) consisted of all subjects who received at least one dose of study medication. Subjects for whom dose verification could not be established were included, with the assumption that they took at least one dose of study medication.

The Endometrial cohort (discussed later in this review) consisted of all treated subjects who received at least one dose of study medication and had an endometrial biopsy performed at both baseline and at the end of treatment.

The “On-treatment” pregnancy rate was calculated using the Pearl Index and life table analyses for the “compliant-use” pregnancy rate, “the typical-use” pregnancy rate (from the PITT cohort) and the “all-users” pregnancy rate (ITT cohort). For the “compliant-use” and “typical-use” pregnancy rates in the PITT cohort, all cycles in which the subject reported using another birth control method (BCM) were not included in the analysis. Any pregnancy that occurred during a partially completed cycle was included in the Pearl Index calculation and the cycle in which the pregnancy occurred was considered a complete cycle.

Within the PITT cohort, subsets of subjects were created based on body weight and “compliant use” with oral contraceptives. For pregnancy calculations in the PITT cohort, subgroup analyses were done for subjects defined as “compliant-use” subjects and for subjects with body weight < 90 kg at the screening visit. Compliant-use was defined by eliminating all cycles in which a subject skipped two or more consecutive pills or had a pattern of substantial non-compliance with study medication, or used a protocol prohibited concomitant medication that may interact with OC therapy. Substantial non-compliance was defined as an overall pill compliance (based on a combination of the drug accountability and the electronic diary) of less than 80%.

Medical Reviewer’s Comment

- *The primary efficacy endpoint was the pregnancy rate as calculated by the Pearl Index in the “Typical-Use” PITT cohort in which no other birth control method was used.*

Pregnancy Testing/Assessment

All urine pregnancy tests were performed using the ~~_____~~ Pregnancy test kit. Urine pregnancy tests were conducted at the Screening Visit, at randomization (Visit 1), every clinic visit, and at the completion of therapy or upon early withdrawal from the study. All subjects were followed for three months following completion of the study or early withdrawal for the occurrence of pregnancy.

Demographics

The demographics are presented in the following two tables. Table 10 represents the entire ITT population. Table 11 focuses on the 18-35 age group on which the primary efficacy analysis is based.

Table 10 Demographic Information at Screening, ITT Population (Subjects with at Least One Complete Cycle on Treatment), Study PSE-302

	DP3-84/30 (N=73)	DP3-84/10 (N=80)	DP3-25/30 (N=84)	Nordette (N=88)	Total (N=325)
Mean Age (yrs)	27.9	26.9	27.1	26.9	27.2
Mean Weight (lbs)	152.7	155.7	154.7	159.0	155.7
Race					
African-American	9 (12.3%)	14 (7.5%)	17 (20.2%)	12 (13.6%)	52 (16.0%)
Asian	4 (5.5%)	2 (2.5%)	3 (3.6%)	3 (3.4%)	12 (3.7%)
Caucasian	51 (69.9%)	54 (67.5%)	52 (61.9%)	57 (64.8%)	214 (65.8%)
Hispanic	7 (9.6%)	9 (11.3%)	10 (11.9%)	13 (14.8%)	39 (12.0%)
Other	2 (2.7%)	1 (1.3%)	2 (2.4%)	3 (3.4%)	8 (2.5%)
Smoking Status					
Non-Smoker	57 (78.1%)	64 (80.0%)	67 (79.8%)	73 (83.0)	261 (80.3%)
Smoker	16 (21.9%)	16 (20.0%)	17 (20.2%)	15 (17.0%)	64 (19.7%)
Prior OC Usage					
Continuous User ¹	45 (61.6%)	51 (63.8%)	54 (64.3%)	43 (48.9%)	193 (59.4%)
Prior User ²	25 (34.2%)	23 (28.8%)	25 (29.8%)	34 (38.6%)	107 (32.9%)
Fresh Start ³	3 (4.1%)	6 (7.5%)	5 (6.0%)	11 (12.5%)	25 (7.7%)

¹ Had history of OC use prior to enrollment

² Had history of OC use, but not within six months prior to enrollment

³ Had no prior history of OC use

Source: NDA 21-840, Clinical Study Report, Page 66

Medical Reviewer's Comment

- Study PSE-302 had a much larger percentage of Hispanic subjects (12.0%) compared to Study PSE-301 (4.9%).

Table 11 Demographic Information at Screening, PITT Population (Subjects 18-35 Years of Age with at Least One Complete Cycle on Treatment), Study PSE-302

	DP3-84/30 (N=67)	DP3-84/10 (N=73)	DP3-25/30 (N=75)	Nordette (N=76)	Total (N=291)
Mean Age (yrs)	27.0	25.9	25.8	25.1	25.9
Mean Weight (lbs)	152.0	152.8	154.9	157.9	154.5
Race					
African-American	8 (11.9%)	12 (16.4%)	16 (21.3%)	11 (14.5%)	47 (16.2%)
Asian	4 (6.0%)	2 (2.7%)	3 (4.0%)	3 (3.9%)	12 (4.1%)
Caucasian	46 (68.7%)	49 (67.1%)	44 (58.7%)	47 (61.8%)	186 (63.9%)
Hispanic	7 (10.4%)	9 (12.3%)	10 (13.3%)	12 (15.8%)	38 (13.1%)
Other	2 (3.0%)	1 (1.4%)	2 (2.7%)	3 (3.9%)	8 (2.7%)
Smoking Status					
Non-Smoker	53 (79.1%)	57 (78.1%)	60 (80.0%)	61 (80.3%)	231 (79.4%)

Smoker	14 (20.9%)	16 (21.9%)	15 (20.0%)	15 (19.7%)	60 (20.6%)
Prior OC Usage					
Continuous User ¹	40 (59.7%)	46 (63.0%)	49 (65.3%)	36 (47.4%)	171 (58.8%)
Prior User ²	24 (35.8%)	21 (28.8%)	21 (28.0%)	29 (38.2%)	95 (32.6%)
Fresh Start ³	3 (4.5%)	6 (8.2%)	5 (6.7%)	11 (14.5%)	25 (8.6%)

¹ Had history of OC use prior to enrollment

² Had history of OC use, but not within six months prior to enrollment

³ Had no prior history of OC use

Source: NDA 21-840, Clinical Study Report, Page 68

Subject Disposition

A total of 380 subjects were randomized in a 1:1:1:1 fashion to DP3-84/30, DP3-84/10, DP3-25/30, or Nordette®-28. Among those randomized, a total of 372 actually took at least one dose of study medication. A total of 325 of the 372 (84.4%) subjects who started treatment completed at least one cycle of treatment. Of the 372 treated subjects who completed at least one cycle of treatment, 291 were between 18 and 35 years of age.

- DP3-84/30: 96 subjects were randomized and 95 subjects were treated.
- **DP3-84/10**: 95 subjects were randomized and 95 subjects were treated.
- DP3-25/30: 94 subjects were randomized and 89 subjects were treated.
- Nordette®-28: 95 subjects were randomized and 93 subjects were treated.

Table 12 summarizes the number of randomized subjects by treatment group included in each of the subject cohorts.

Table 12 Subject Cohorts, Study PSE-302

	DP3-84/30 (N=96)		DP3-84/10 (N=95)		DP3-25/30 (N=94)		Nordette (N=95)		Total (N=380)	
	N	%	N	%	N	%	N	%	N	%
Randomized	96	100	95	100	94	100	95	100	380	100
Treated Subjects (Safety)	95	99.0	95	100	89	94.7	93	97.9	372	97.9
Treated at Least One Complete Cycle (ITT)										
< 90 kg	73	76.0	80	84.2	84	89.4	88	92.6	325	85.5
≥ 90 kg	67	69.8	68	71.6	72	76.6	71	74.7	278	73.2
≥ 90 kg	6	6.3	12	12.6	12	12.8	17	17.9	47	12.4
ITT and 18-35 Years of Age (PITT)										
< 90 kg	67	69.8	73	76.8	75	79.8	76	80.0	291	76.6
≥ 90 kg	61	63.5	63	63.3	64	68.1	62	65.3	250	65.8

Source: NDA 21-840, Clinical Study Report, Page 58

Among all treated subjects, the most common reasons for discontinuation were AEs (12.9%). The DP3-84/30 group was associated with the highest rates of withdrawal (57.9%) with

comparable rates of withdrawal seen for the other three groups (See Table 14 below). Bleeding and/or spotting were cited as the reason for study discontinuation both through AEs and subject decision to withdraw. Bleeding and/or spotting as an AE leading to discontinuation occurred in 8 (8.4%) of the DP3-84/30, 7 (7.4%) of the DP3-84/10, 5 (5.6%) of the DP3-25/30 and 1 (1.1%) of the Nordette treated subjects. Bleeding and/or spotting cited as part of the subject decision to withdraw occurred in 1 (1.1%) of DP3-84/30, 2 (2.1%) of DP3-84/10, 2 (2.2%) of DP3-25/30 and 0 (0.0%) of Nordette treated subjects.

Table 13 Disposition of All Treated Subjects (Safety)

	DP3-84/30 (N=95)		DP3-84/10 (N=95)		DP3-25/30 (N=89)		Nordette (N=93)		Total (N=372)	
	N	%	N	%	N	%	N	%	N	%
Safety Cohort	95	100.0	95	100.0	89	100.0	93	100.0	372	100.0
Discontinued Study	55	57.9	49	51.6	45	50.6	46	49.5	195	52.4
Primary Reasons for Discontinuation:										
Adverse Event	20	21.1	11	11.6	11	12.4	6	6.5	48	12.9
Patient Decision	8	8.4	8	8.4	7	7.9	5	5.4	28	7.5
Non-Compliance with Study Protocol	6	6.3	4	4.2	5	5.6	10	10.8	25	6.7
Lost to Follow-Up	15	15.8	20	20.1	20	22.5	21	22.6	76	20.4
Pregnancy	1	1.1	1	1.1	0	0.0	1	1.1	3	0.8
Investigator's Discretion	1	1.1	0	0.0	0	0.0	0	0.0	1	0.3
Other/Unknown	4	4.2	5	5.3	2	2.2	3	3.2	14	3.8

Source: NDA 21-840, Clinical Study Report, Page 59

Medical Reviewer's Comments

- *As mentioned above, of the 11 subjects in the DP3-84/10 arm who withdrew from the study due to an adverse event, 9 of these withdrawals were related to bleeding and/or spotting (82%).*
- *Two subjects of the 8 in the "Patient Decision" group cited bleeding and/or spotting as contributing to the decision to withdraw.*
- *Eleven of the total 49 discontinuations were bleeding and/or spotting related (22.4%).*
- *Discontinuation rates were similar in all study arms and most were due to adverse events. Unfortunately, since Seasonale was not used as a comparator, we cannot assess discontinuation rates relative to the already approved extended cycle product.*

Primary Efficacy Assessments and Endpoints

The efficacy calculation is based on completed cycles in the 18-35 year age range and excludes cycles where other birth control methods were utilized (PITT cohort). During this study, a total of eight subjects who enrolled in the study became pregnant. Four of these pregnancies were determined to be "On-treatment" and four "Off-treatment".

Table 14 Pearl Index Calculation of Treatment Failure Rates in Subjects 18-35 years of Age With at Least One Complete Cycle of Treatment (PITT) and Excluding Cycles in Which Another Birth Control Method Was Used, Study PSE-302

Treatment Group	Number of Cycles	Number of 28-Day Patient Months	Number of "On-Drug" Pregnancies	Pearl Index
DP3-84/30	153	497.25	1	2.61
DP3-84/10	166	539.50	1	2.41
DP3-25/30	606	606.00	0	0.00
Nordette	591	591.00	2	4.40

Source: NDA 21-840, Clinical Study Report, Page 77

Medical Reviewer's Comments

- *It should again be noted that condom use was permitted in the study. The daily electronic patient diary, however, did not provide a mechanism for the subject to differentiate from other types of birth control methods which may have been used.*
- *The number of complete 28-day patient-months where condom use was not excluded for DP3-84/10 was 705.25.*
- *By way of comparison, the Pearl Index of the already approved Seasonale is 1.98 per 100 women-years of use.*
- *In this supportive study with only 137 cycles, the 91-day extended regimen combination oral contraceptive DP3-84/10 regimen (Seasonique) was given for one year in women ages 18-35 desiring pregnancy prevention. When no other method of contraception was used, the Pearl Index in this cohort was 2.41 per 100 women-years of use. The FDA statistician agreed with this calculation.*
- *Since the sample size chosen for this study was intended to provide sufficient before and end of treatment endometrial biopsy information, the number of cycles of exposure for the Pearl Index calculations is much smaller than what would be required in a standard efficacy study of oral contraception. Thus, the Pearl Index calculations presented in Study PSE-302 may not be representative estimates of the true method failure rate and is therefore treated in this review as a supportive study only.*

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Pregnancy Case Listings for All Treated Subjects

Table 15 Reported Pregnancies in All Treatment Groups, Study PSE-302

Drug Site/ Pt #	Age/ Wt. in lbs.	User Type	Drug Start Date	Drug Stop Date	Date of Positive Preg Test	Conception Date	Applicant Considers Preg On/Off Treatment*	MO Considers Preg On/Off Treatment	MO Evaluation of Compliance
DP3-84/10 61/459	30/ 127	C	11/17/02	8/11/03	8/12/03	6/4/03	On	On	Compliant
DP3-84/30 66/1018	23/ 128	C	12/22/02	9/17/03	9/17/03	8/5/03	On	On	Compliant
DP3-25/30 61/445	31/ 158	F	10/20/02	7/7/03	11/4/03	9/23/03	Off	Off	N/A
61/481	32/ 103	C	12/29/02	3/1/02	9/11/03	8/10/03	Off	Off	N/A
67/1188	33/ 130	C	11/3/02	10/4/03	1/26/04	1/11/04	Off	Off	N/A
Nordette 61/467	20/ 135	P	11/24/02	1/3/03	12/31/02	12/13/02	On	On	Non- Compliant
62/566	27/ 119	P	10/13/02	11/3/02	1/6/03	11/21/02	No	No	N/A
66/1003	30/ 162	C	8/18/02	8/16/03	9/10/03	8/12/03	On	On	Compliant

* First day of study drug use to 14 days following last dose date

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 21-840, Clinical Study Report, Adapted from Page 103 and the narrative summaries

Medical Reviewer's Comments

- *This reviewer agrees with the Applicant's designation of on or off treatment determinations at the time of conception.*
- *Although calculations for the rate of pregnancy, using the Pearl Index, were done for Study PSE-302, the ability to interpret these results is limited due to the small number of cycles exposed to treatment (137).*

6.1.4 Clinical Microbiology

This study drug is not an antimicrobial so this section is not applicable.

6.1.5 Efficacy Conclusions

Utilizing the most conservative criteria for assessing the Pearl Index, Seasonique has an acceptable pregnancy rate.

Medical Reviewer's Comment

- *This drug without the seven days of EE 0.01 mg monotherapy is identical to the recently approved extended cycle combination oral contraceptive, Seasonale. The Pearl Index in the Seasonale label is 1.98 per 100 women-years of use. There is no theoretical reason to assume that the addition of the seven days of EE 10 mcg monotherapy will impede or enhance the contraceptive efficacy of the Seasonique formulation. The benefit to the patient of the seven days of EE monotherapy in terms of efficacy is not addressed in Study PSE-302.*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Two one year, multicenter, randomized, open-label, Phase 3, clinical studies were performed to evaluate the safety of DP3-84/10. PSE-301 was a large, multicenter study of over 2000 subjects designed to assess the efficacy and safety of two 91-day extended regimen doses (DP3-84/30 and DP3-84/10) with over 1000 subjects per treatment group. No regulatory claims are being sought for DP3-84/30. PSE-302 was a smaller, multicenter study designed to obtain baseline and end of treatment endometrial biopsy data on the same two DP3 91-day extended regimen doses used in PSE-301. PSE-302 was conducted as a supportive study to PSE-301. PSE-302 also included two additional exploratory treatment arms: a 28-day DP3 -25/30 regimen and a 28-day Nordette regimen (approximately 90 subjects in each of the four treatment arms).

Medical Reviewer's Comments

- *Combination oral contraceptive products containing ethinyl estradiol and levonorgestrel have been marketed for decades worldwide, and in the United States since 1968 (Ovral).*
- *Levonorgestrel containing oral contraceptives are generally considered to be associated with a lower risk for the development of thrombotic or thromboembolic adverse events than oral contraceptives containing third generation progestins (e.g., desogestrel, gestodene, norgestimate).*
- *There is a very large safety database for both of the active components of Seasonique (ethinyl estradiol and levonorgestrel). 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 ethinyl estradiol and levonorgestrel is found in the Appendix Section 10.1.1.1. These products include Ovral, Lo-Ovral, Nordette, Triphasil, Alesse, and Levlite. In addition, levonorgestrel is used alone as a contraceptive in Norplant, Norplant II, Mirena (an IUD), and Plan B (an emergency contraceptive).*
- *Duramed did not submit any new nonclinical pharmacokinetic or toxicology studies in support of the current application. The Applicant concluded that the safety of Seasonique could be adequately demonstrated without additional nonclinical studies because*

sufficient data already existed supporting the safety of Seasonale and this data also supports the safety of the new Seasonique dosing regimen. The Applicant believes that the “minor” difference of replacing the placebo tablets in Seasonale with the ethinyl estradiol 10 mcg tablets in Seasonique does not impact on the safety profile of the combination tablets of levonorgestrel and ethinyl estradiol.

Safety was evaluated in the following manner for Studies PSE-301 and PSE-302:

- Subjects were informed 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 electronic diary additionally captured typical symptoms occurring around the time of a withdrawal period with weekly questions.
- Withdrawal type symptoms were also evaluated in the quality of life questionnaires
- 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

Table 16 Extent of Subject Exposure to Study Drugs, Safety Cohort*

Months on Study	DP3-84/30 (N=1108)		DP3-84/10 (N=1101)		DP3-25/30 (N=89)		Nordette (N=93)	
	N	%	N	%	N	%	N	%
≤1	88	7.9	77	7.0	5	5.6	9	9.7
>1-2	109	9.8	81	7.4	4	4.5	5	5.4
>2-3	74	6.7	69	6.3	6	6.7	3	3.2
>3-4	77	6.9	78	7.1	5	5.6	3	3.2
>4-5	43	3.9	41	3.7	6	6.7	2	2.2
>5-6	40	3.6	46	4.2	5	5.6	4	4.3
>6-7	51	4.6	52	4.7	4	4.5	3	3.2
>7-8	24	2.2	21	1.9	4	4.5	3	3.2
>8-9	14	1.3	23	2.1	2	2.2	4	4.3
>9-10	29	2.6	34	3.1	2	2.2	3	3.2
>10-11	12	1.1	11	1.0	1	1.1	2	2.2
>11-12	17	1.5	12	1.1	1	1.1	3	3.2
>12	530	47.8	556	50.5	44	49.4	49	52.7
Completed Study	519	46.8	546	49.6	44	49.4	47	50.5

*Safety Cohort: those who received at least one dose of study drug, whether or not the subjects ever returned for any post-baseline study visit.

Source: Original NDA 21-840, Integrated Summary of Safety, Page 17

Medical Reviewer's Comment

- *The above table lists calendar months of exposure to study drugs. Of the 556 patients listed as having > 12 months of exposure to DP3-84/10, 546 fully completed treatment in the DP3-84/10 arm. . This exceeds the recommended subject exposure of 200 women for ≥ 12 months in order to assess safety.*

7.1.1 Deaths

There were no reported deaths in any treatment group in Studies PSE-301 or PSE-302.

7.1.2 Other Serious Adverse Events

Overall, 24 of the 1108 (2.2%) subjects treated with DP3-84/30, 25 of the 1101 (2.3%) subjects treated with DP3-84/10, 1 of the 89 (1.1%) subjects treated with DP3-23/30 and three of the 93 (3.2%) subjects treated with Nordette reported one or more serious adverse events. A total of nine subjects discontinued from the study (five on DP3-84/30 and four on DP3-84/10) as a result of a SAE.

For DP3-84/30 the SAEs contributing to discontinuation included: anemia (Subject 01/210), adjustment disorder/depressed mood (Subject 19/3855), convulsions (Subject 28/5637), anxiety/depression (Subject 33/6612), and lymphadenopathy (Subject 63/686).

For **DP3-84/10 (Seasonique)**, the SAEs leading to discontinuation included malignant melanoma (Subject 1/0322), migraine (Subject 2/0417), foot fracture (Subject 16/3210), and hypoxia (Subject 63/0654).

None of the SAEs reported in Studies PSE-301 and PSE-302 were judged by the investigators to have more than a "possible" relationship to study drug.

Medical Reviewer's Comment

- *This reviewer concurs that the serious adverse events in these studies were possibly but not necessarily related to study drug administration.*

Serious adverse events reported for the Seasonique treatment group are listed in Table 17 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. Serious adverse events were reported for 25 Seasonique subjects.

Table 17 Serious Adverse Events DP3-84/10 (Seasonique) Treatment Group, Studies PSE-301 and PSE-302

Site #	Subject #/ Study #	Serious AE	Relationship to Study Drug	Subject Discontinued
1	0322/301	Malignant Melanoma	None	Yes
2	0417/301	Migraine	Possible	Yes
3	0623/301	Cholelithiasis Pancreatitis	Possible Possible	No No
6	1215/301	Appendicitis	None	No
9	1828/301	Pelvic Inflammatory Disease	None	No
10	2025/301	Cholecystitis Cholelithiasis	Possible Possible	No No
13	2623/301	Appendicitis Abscess at Incision Site	None None	No No
13	2679/301	Urinary Tract Obstruction	None	No
13	2744/301	Cholelithiasis Pancreatitis	None None	No No
14	2870/301	Cholelithiasis	Remote	No
14	2885/301	Sialoadenitis	None	No
16	3210/301	Foot Fracture	None	Yes
18	3604/301	Cholelithiasis	Possible	No
18	3617/301	Abdominal Pain	Remote	No
19	3816/301	Appendicitis	None	No
20	4002/301	Appendicitis	None	No
20	4008/301	Herniated Disc	None	No
20	4019/301	Premature Labor	None	No
21	4268/301	Depression Suicidal Ideation	None None	No No
25	5027/301	Traffic Accident	None	No
29	5871/301	Intrauterine Death	None	No
29	5874/301	Intestinal Obstruction Urinary Tract Infection	None None	No No
61	0459/302	Intrauterine Death	None	No
63	0654/302	Hypoxia	None	Yes
67	1185/302	Major Depressive Disorder	Remote	No

Source: NDA 21-840, Integrated Summary of Safety, Page 34

Several case reports were reviewed for possible causality.

Subject 0002-0417 was a fresh start user of oral contraceptives. Her medical history included epilepsy since 1997 with the last known seizure occurring in September, 2002. She also had a positive family history for migraine headaches. She began taking DP3-84/10 on December 9, 2002. On _____ she experienced tunnel vision in her left eye, which progressed to

decreased vision bilaterally. She also experienced numbness on the left side of her body, photophobia, phonophobia, and a headache. She was admitted to the hospital that same day with a diagnosis of migraine headache with aura possibly related to study drug. Her symptoms resolved in approximately four hours. A CAT Scan, MRI, and chest x-ray were negative and results of laboratory tests were unremarkable. She was discharged on _____. She took her last dose of study drug on April 9, 2003 and discontinued from the study due to the migraine headache.

Subject 0013-2679 was a prior user of oral contraceptives but not within six months prior to study enrollment. Her medical history included right ureteral stone removal and recurrent urinary tract infections. She began taking DP3-84/10 on August 25, 2002. On _____, she was hospitalized for a urinary tract obstruction. On that same day a right uretero neocystostomy was performed to correct her urinary reflux. The narrative is unclear as to the cause of the urinary tract obstruction but the investigator felt that it was not related to the study drug. The subject discontinued the study on April 11, 2003 due to inconvenience associated with the study visits.

Subject 0013-2744 was a 40 year old Caucasian, non-smoker. She was a continuous user of oral contraceptives. Her medical history was positive for cholelithiasis which was diagnosed in 2002. She began taking DP3-84/10 on March 9, 2003. On _____, she was admitted to the hospital with acute right upper quadrant pain associated with nausea and vomiting. Ultrasound revealed cholelithiasis and a cholecystectomy was performed on _____. She recovered without complications. She continued on study drug and on _____ she was admitted to the hospital complaining of abdominal pain which was diagnosed as pancreatitis. She recovered and was discharged on _____. Study medication was not interrupted for this event. The subject took her last dose of study medication on March 6, 2004 and completed the final study visit on February 27, 2004.

Subject 0018-3617 was a continuous pill user having used Levlite® during the menstrual cycle prior to enrollment. Her medical history included a history of gall bladder disease. She began taking study drug on June 30, 2002. On _____ she was admitted to the hospital complaining of right upper quadrant abdominal pain with nausea and diarrhea. The pain resolved on February 5, 2003. No definitive diagnosis was made. The subject completed the study and took her last dose of study drug on June 28, 2003.

Subject 0029/5871 was a prior user of oral contraceptives. She began taking DP3-84/10 on September 22, 2002. She completed the study and took her last dose of study drug on September 20, 2003. The final study visit was conducted on December 9, 2003, at which time she had a negative urine pregnancy test. She reported a positive urine pregnancy test on December 29, 2003 and subsequently miscarried.

Subject 0063/0654 was a continuous user of oral contraceptives. Her medical history included a family history of sickle cell trait. She began taking DP3-84/10 on August 4, 2002. On _____ she presented to the emergency room complaining of shortness of breath and chest pain, and was admitted to the hospital that same day. Arterial blood gases revealed hypoxia. Chest x-

ray showed no active pulmonary disease. Ventilation/perfusion lung scan showed no evidence of pulmonary embolism, and a CT scan of the chest was negative and her lungs were clear. Ultrasounds of the extremities were negative, ruling out DVT. An echocardiogram was normal with the exception of trace tricuspid insufficiency. Clinical laboratory results were normal with the exception of a CPK of 308 IU/L (0-250). The event was considered resolved and she was discharged on _____ with a discharge diagnosis of hypoxemia (not related to study drug) secondary to smoking and bronchitis. She took her last dose of study medication on September 30, 2002.

Medical Reviewer’s Comments

- *This reviewer would reclassify Subject 0013-2744 as having cholecystitis possibly related to study drug administration.*
- *There are no new signals of unexpected serious adverse events related to the extended use of DP3-84/10.*

Serious adverse events reported for the DP3-84/30 treatment group are listed in Table 18 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. Serious adverse events were reported for 24 DP3-84/30 subjects.

Table 18 Serious Adverse Events DP3-84/30 Treatment Group, Studies PSE-301 and PSE-302

Site #	Subject #/ Study #	Serious AE	Relationship to Study Drug	Subject Discontinued
1	0210/301	Anemia	Possible	Yes
1	0269/301	Postoperative Complications	None	No
1	0295301	Intervetebral Disc Herniation	None	No
4	0803/301	Varicella	None	No
8	1612/301	Albinism	None	No
		Blindness	None	No
		Premature Baby	None	No
10	2030/301	Spontaneous Abortion	None	No
13	2658/301	Cervical Cancer Stage 0	None	No
13	2673301	Jaw Fracture	None	No
13	2738/301	Pelvic Inflammatory Disease	None	No
18	3627/301	Concussion	None	No
		Convulsions	None	No
19	3820/301	Spontaneous Abortion	None	No
19	3855/301	Adjustment Disorder with Depressed Mood	Remote	Yes
20	4004/301	Obesity	None	No
21	4253/301	Myasthenia Gravis activated	Possible	No

25	5006/301	Bacterial Infection	None	No
26	5211/301	Uterine Fibroids Aggravated	Possible	No
27	5403/301	Intervetebral Disc Herniation Sciatica	None None	No No
27	5426/301	Cerebrospinal Fluid Leakage Intervetebral Disc Herniation Wound Infection	None None None	No No No
28	5637/301	Convulsions	None	Yes
31	6301/301	Suicide Attempt	Remote	No
33	6612/301	Anxiety Depression	Remote Remote	Yes Yes
35	7020/301	Chest Pain Palpitations Tachycardia	None None None	No No No
61	0457/302	Bipolar Disorder Major Depressive Disorder	Remote Remote	No No
63	0686/302	Lymphadenopathy	None	Yes

Source: NDA 21-840, Integrated Summary of Safety, Page 33

Several case reports were reviewed.

Subject 0001/0210 discontinued therapy secondary to anemia reportedly due to an atrophic endometrium and fibroids. This event was considered “possibly” related to study drug.

Subject 0019/3855 discontinued DP3-84/30 due to adjustment disorder and depression. She received no medical treatment for her depression, which was felt to be situational and secondary to the recent breakup with her boyfriend. The relationship between this event and the study drug was considered remote.

Subject 0028/5637 discontinued DP3-84/30 secondary to convulsions. Neurological evaluation suggested that the convulsion may have been secondary to migraines and marijuana inhalation. Multiple CAT scans of her brain, with and without contrast, were normal. The event was considered not related to study drug.

Subject 0033/6612 discontinued DP3-84/30 due to anxiety and depression. The subject was treated but lost to follow-up. The relationship to study drug was considered remote.

Subject 0063/0686 discontinued DP3-84/30 treatment in Study PSE-302 secondary to lymphadenopathy that was determined to be related to a viral syndrome and not related to study drug.

Medical Reviewer’s Comment

- *There are no new signals of unexpected serious adverse events reported for the DP3-84/10 arm.*

Serious adverse events reported for the DP3-25/30 and Nordette treated subjects are listed in Table 19 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. Serious adverse events were reported for one DP3-25/30 treated subject and three Nordette treated subjects.

Table 19 Serious Adverse Events DP3-25/30 and Nordette Treatment Groups, Studies PSE-302

Site #	Subject #	Drug	Serious AE	Relationship to Study Drug	Subject Discontinued
62	0548	DP3-25/30	Dental Discomfort	None	No
61	0489	Nordette	Lower Limb Fracture	None	No
67	1182	Nordette	Appendicitis	None	No
67	1205	Nordette	Peritonitis Renal Calculi, Aggravated	None None	No No

Source: NDA 21-840, Integrated Summary of Safety, Page 34

Medical Reviewer's Comment

- *None of the four subjects in Table 21 discontinued the study due to a SAE.*

7.1.3 Dropouts and Other Significant Adverse Events

Refer to Tables 20 and 21.

7.1.3.1 Overall profile of dropouts

Table 20 Disposition of All Treated Subjects in Studies PSE-301 and PSE-302 (Safety Cohort)

	DP3-84/30 (N=1108)		DP3-84/10 (N=1101)		DP3-25/30 (N=89)		Nordette (N=93)		Total (N=2391)	
	N	%	N	%	N	%	N	%	N	%
Safety Cohort	1108	100.0	1101	100.0	89	100.0	93	100.0	2391	100.0
Discontinued Study	589	53.2	555	50.4	45	50.6	46	49.5	1235	51.7
Primary Reason										
Adverse Event	220	19.9	175	15.9	11	12.4	6	6.5	412	17.2

Subject decision	121	10.9	138	12.5	7	7.9	5	5.4	271	11.3
Non-Compliance	42	3.8	42	3.8	5	5.6	10	10.8	99	4.1
Lost to Follow-Up	164	14.8	169	15.3	20	22.5	21	22.6	374	15.6
Pregnancy	19	1.7	6	0.5	0	0.0	1	1.1	26	1.1
Investigators Discretion	2	0.2	2	0.2	0	0.0	0	0.0	4	0.2
Other/Unknown	21	1.9	23	2.1	2	2.2	3	3.2	49	2.0

Source: NDA 21-840, Integrated Summary of Safety, Page 12

7.1.3.2 Adverse events associated with dropouts

The overall integrated study discontinuation rates due to adverse events for DP3-84/30, DP3-84/10, DP3-25/30, and Nordette were 19.9%, 15.9%, 12.4%, and 6.5% respectively.

A total of 80 subjects (3.35%) discontinued from the study due to intermenstrual bleeding (3.27% of the Seasonique group). Of the 36 subjects in the Seasonique group who discontinued the study, only one subject had a hemoglobin (Hb) lower than the lower limit of normal (i.e., 11.6 g/dL). Subject 19/3856 had a Hb of 12.1 at baseline and 11.4 g/dL at the end of the study.

Evaluation of Hb results, regardless of whether any subject discontinued due to intermenstrual bleeding, shows that the treatment groups had similar small median changes from baseline to end of treatment. A total of 34 subjects had Hb values below the lower limit of normal (i.e., 11.6 g/dL) at the end of study visit.

Table 21 provides an integrated display of all adverse events reported to lead to discontinuation from Study PSE-301 and Study PSE-302.

Table 21 Adverse Events Leading to Discontinuation from Study-All Treated Subjects, Safety Cohort

Discontinuation Reason*	DP3-84/30 (N=1108)		DP3-84/10 (N=1101)		DP3-25/30 (N=89)		Nordette (N=93)	
	N	%	N	%	N	%	N	%
Intermenstrual Bleeding	39	3.52	36	3.27	5	5.62	0	0.00
Menorrhagia	41	3.70	29	2.63	0	0.00	0	0.00
Menstruation Irregular	3	0.27	1	0.09	0	0.00	0	0.00
Dysmenorrhea	6	0.54	5	0.45	0	0.00	0	0.00
Breast Tenderness/ Pain	6	0.54	5	0.45	0	0.00	0	0.00
Breast Mass/Cyst	2	0.18	0	0.00	0	0.00	0	0.00
Weight Gain	22	1.99	27	2.45	1	1.12	0	0.00
Blood Pressure Increase	2	0.18	1	0.09	0	0.00	0	0.00
Mood Swings	18	1.62	17	1.54	1	1.12	0	0.00
Depression	6	0.54	6	0.54	1	1.12	0	0.00
Decreased Libido	8	0.72	5	0.45	0	0.00	0	0.00

Irritability	10	0.90	2	0.18	0	0.00	0	0.00
Acne	13	1.17	11	1.00	1	1.12	0	0.00
Abdominal Distension	14	1.26	8	0.73	0	0.00	0.0	0.00
Nausea	10	0.90	5	0.45	1	1.12	1	1.08
Headache NOS	12	1.08	4	0.36	0	0.00	1	1.08
Migraine NOS	8	0.72	2	0.18	0	0.00	0	0.00
Fatigue	8	0.72	6	0.54	1	1.12	0	0.00
Arthralgia	3	0.27	3	0.37	0	0.00	0	0.00

*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 21-840, Integrated Summary of Safety, Page 26

Medical Reviewer's Comment

- *Across both studies (PSE-301 and PSE-302) 6.3 % of DP3-84/10 (Seasonique) subjects discontinued, at least in part, due to bleeding and/or spotting. In NDA 21-544 (Study SEA-301) 6.1% of Seasonale treated subjects (N=397) discontinued for the same reason.*

7.1.3.3 Other significant adverse events

For DP3-84/10 (Seasonique), the most significant adverse events in terms of incidence were the bleeding problems of menorrhagia and intermenstrual bleeding.

7.1.4 Other Search Strategies

No other search strategies were employed.

7.1.5 Common Adverse Events

Table 22 shows the incidence rates for the most frequently reported treatment-emergent adverse events (incidence rates of 5% or greater) for the safety cohort (i.e., all treated subjects).

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.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Use of the MedDRA categorization is appropriate to tabulate adverse events.

7.1.5.3 Incidence of common adverse events

See Table 22.

7.1.5.4 Common adverse event tables

Table 22 Incidence of Treatment Emergent Adverse Events Occurring in 5% or More of Treated Subjects, Studies PSE-301 and PSE-302

MedDRA Term	DP3-84/30 (N=1108)		DP3-84/10 (N=1101)		DP3-25/30 (N=89)		Nordette (N=93)		Total (N=2391)	
	N	%	N	%	N	%	N	%	N	%
Intermenstrual Bleeding	137	12.36	126	11.44	9	10.11	2	2.15	274	11.46
Menorrhagia	85	7.67	62	5.63	2	2.25	2	2.15	151	6.32
Nasopharyngitis	97	8.75	80	7.27	12	13.48	12	12.90	201	8.41
Sinusitis	64	5.78	72	6.54	4	4.49	3	3.23	143	5.98
Urinary Tract Infection	36	3.25	49	4.45	5	5.62	7	7.53	97	4.06
Acne	43	3.88	60	5.45	2	2.25	1	1.08	106	4.43
Nausea	51	4.60	48	4.36	2	2.25	7	7.53	108	4.52
Headache	56	5.05	42	3.81	7	7.87	3	3.23	108	4.52

Source: NDA 21-840, Integrated Summary of Safety, Page 23

Medical Reviewer's Comments

- *The difference in the rates of specific adverse events across the study (e.g., nasopharyngitis, nausea, urinary tract infection) may be due to the variations in sample size among the cohorts. Despite this variance in sample size however, intermenstrual bleeding (defined as any report of bleeding or spotting that occurred during the active pill phase, regardless of severity) was reported as an adverse event with a higher incidence for all DP3 groups than for Nordette. Menorrhagia (defined as heavy or prolonged bleeding during the withdrawal period) was also reported at a higher incidence for the DP3-84/30 (7.67%) and DP3-84/10 (5.63%) regimens than for the DP3-25/30 (2.25%) or Nordette (2.15%). It is reasonable to expect a greater propensity for menorrhagia in some subjects when the interval between cycles is increased.*
- *The adverse event profile is similar to that of the already approved Seasonale (NDA 21-544). In the Seasonale clinical trials, the most common adverse events were nasopharyngitis (21.9%), headache (20.6%) and menorrhagia (11.6%). In the Seasonale NDA however, the term "menorrhagia" also included bleeding that occurred during the active pill phase.*

7.1.5.5 Identifying common and drug-related adverse events

Annual Hormone Exposure

Extended cycle oral contraception regimens inherently provide for the exposure of a higher total annual dose of both LNG and EE than conventional 28 day oral contraceptive regimens containing equivalent amounts. As shown in Table 23, the total annual dose of both active ingredients in Seasonique falls within the range of other approved combination oral contraceptives containing LNG and EE.

Table 23 Comparison of Total Annual Exposure to EE and LNG with Seasonique Compared to Other Approved Oral Contraceptives

	Levlite	Nordette	Portia	LoOvral	Seasonale	Seasonique	Ovral
EE dose/combination tablet (mg)	0.02	0.03	0.03	0.03	0.03	0.03	0.05
LNG dose/combination tablet (mg)	0.10	0.15	0.15	0.15 ^a	0.15	0.15	0.25 ^b
EE dose/tablet (mg)	0	0	0	0	0	0.01	0
# of active tablets/cycle	21	21	21	21	84	91	21
# of cycles/year	13	13	13	13	4	4	13
# of active tablets/year	273	273	273	273	336	364	273
Total dose EE/year (mg)	5.46	8.19	8.19	8.19	10.08	10.36	13.65
Total dose LNG/year (mg)	27.3	40.95	40.95	40.95	50.4	50.4	68.25

^a Contains 0.3 mg d,l-norgestrel, of which 0.15 mg is the active progestin levonorgestrel

^b Contains 0.5 mg d,l-norgestrel, of which 0.25 mg is the active progestin levonorgestrel

Source: NDA 31-840, Integrated Summary of Benefits and Risks, Table 5

Medical Reviewer's Comments

- *The total annual dose of ethinyl estradiol in the Seasonique formulation is 10.36 mg. In Seasonale, the total ethinyl estradiol annual dose is 10.08 mg. Seasonique is slightly higher in EE but the difference is only 0.28 mg per year.*
- *The total annual dose of LNG found in Seasonique is identical to that found in Seasonale.*
- *The total annual dose of EE and LNG in Seasonique is lower than the total annual dose of LNG and EE found in the approved oral contraceptive, Ovral.*
- *Seasonale was approved for the prevention of pregnancy on September 5, 2003 although there was no proven benefit demonstrated for the extended cycle oral contraceptive regimen concept.*

Cycle Control

Bleeding and/or Spotting

In the submission the Applicant defines bleeding and/or spotting data as follows:

- The total number of bleeding and/or spotting days reported for each 91-day DP3-84/30 or DP3-84/10 extended cycle and the total number of bleeding and/or spotting days recorded for the 28-day Nordette cycle. This number includes bleeding that is both unscheduled (intermenstrual) and scheduled (withdrawal) bleeding.
- The number of “unscheduled” bleeding and/or spotting days (i.e., bleeding and/or spotting during the 84 days of DP3-84/10 and DP3-84/30 active combination therapy or the 21 active pill days of Nordette therapy).

Results for total, unscheduled and scheduled bleeding and/or spotting are calculated for all subjects with at least one complete cycle of therapy (ITT Population).

Medical Reviewer’s Comments

- *In Studies PSE-301 and PSE-302, the most common drug-related adverse event for Seasonique was intermenstrual bleeding. Intermenstrual or “unscheduled” bleeding is unanticipated by the patient and is the most bothersome type of bleeding.*
- *Comparisons made in this review will primarily be made between Seasonique and Seasonale. However these drugs were studied separately in two different studies; not “head to head” in the same study. Therefore any conclusions comparing Seasonale to Seasonique, especially with reference to bleeding, may be subject to “cross study” bias.*

Total Days of Bleeding and/or Spotting

The total number of days of bleeding and/or spotting by cycle is presented for all treated subjects who completed at least one cycle of treatment (ITT Population). The information presented in Table 24 is a summary of the electronic daily diary reports from this population.

Table 24 Total Days of Bleeding and/or Spotting by Cycle (Complete Cycles Only, ITT Population), Studies PSE-301 and PSE-302

Treatment Group	Cycle	N (Subjects with at least one complete cycle)	Mean	Median
DP3-84/30	1	808	18.8	15
	2	663	15.1	10
	3	558	12.5	8.5
	4	457	11.9	7

DP3-84/10	1	829	17.8	14
	2	684	12.6	9
	3	583	10.1	7
	4	486	10.6	7
Nordette	1	84	5.7	5
	2	79	5.0	5
	3	72	4.7	4
	4	69	4.1	4
	5	67	3.9	4
	6	61	4.2	4
	7	59	4.4	4
	8	57	4.2	4
	9	53	4.7	4
	10	52	4.5	4
	11	49	3.9	4
	12	47	3.7	3
	13	45	5.6	5

*Obtained by multiplying the 91-day cycle by the factor (28/91) to adjust for the difference in cycle length compared to a 28-day conventional cycle.

Source: NDA 21-840, Adapted from Table 11.1, Integrated Summary of Safety, Page 47

Medical Reviewer's Comments

- *Comparing Seasonique to Nordette in total bleeding and/or spotting days can be problematic. Nordette is designed to produce a withdrawal or anticipated bleed every 28-days so one would expect total bleeding and/or spotting days to be higher than with the extended 91-day regimens. This would tend to bias against Nordette and make it appear worse than the comparator 91-day regimen for total bleeding and/or spotting days.*
- *Table 24 compares DP3-84/10 (Seasonique) to DP3-84/30 and Nordette. While the bleeding profile appears acceptable, no information is provided as to the benefit of this new formulation over the already approved Seasonale. Therefore a review of NDA 21-544 provides the following data regarding Seasonale.*

Table 25 Mean Total Bleeding and/or Spotting Days Per Subject-Month

Cycle	Seasonique	Seasonale*
1	5.5	5.7
2	3.9	4.6
3	3.1	4.3
4	3.3	3.9

*Seasonale data taken from medical officer's review of NDA 21-544

- *Although the above is taken from cross-study data with inherent bias, Seasonique does appear to have slightly less total bleeding and/or spotting days per subject-month. Seasonale subjects had a mean of 12.3 total number of bleeding and/or spotting days by Cycle 4 compared to a mean of 10.6 total days for Seasonique. Although the total bleeding and/or spotting days is less with Seasonique, the difference between these two drug products does not appear to this reviewer to be clinically significant.*

Unscheduled Bleeding and/or Spotting

The total number of days of unscheduled bleeding and/or spotting by cycle is presented for all treated subjects who completed at least one cycle of treatment (ITT Population). The information presented in Table 26 is a summary of the electronic daily diary reports from this population.

Table 26 Total Days of Unscheduled Bleeding and/or Spotting by Cycle (Complete Cycles Only, ITT Population)

Drug	Cycle	N (Subjects with at least one complete cycle)	Mean	Median
DP3-84/30	1	808	15.7	11.5
	2	663	12.3	7
	3	558	9.9	6
	4	457	9.5	5
DP3-84/10	1	829	14.4	11
	2	684	9.5	5
	3	583	7.3	4
	4	486	7.8	4
Nordette	1	84	2.4	1
	2	79	1.9	1
	3	72	1.8	1
	4	69	1.4	1
	5	67	1.4	1
	6	61	1.5	1
	7	59	1.6	1
	8	57	1.6	1
	9	53	1.9	1
	10	52	1.9	1
	11	49	1.2	1
	12	47	1.0	0
	13	45	2.6	2

* Obtained by multiplying the 91-day cycle by the factor (21/84) to adjust for the difference in cycle length compared to a 28-day conventional cycle.

Source: NDA 21-840, Adapted from Table 11.5, Integrated Summary of Safety, Page 54

Medical Reviewer's Comments

- *Unscheduled or unanticipated bleeding and/or spotting is the most important cycle control parameter to measure as this is what concerns most patients.*
- *For DP3-84/10, the number of days of unscheduled bleeding and/or spotting per month decreased over time over the first three cycles. By the third and fourth cycles, rates were comparable to Nordette.*
- *The Applicant points out that the length of time of active combination pill treatment is greater for the 91-day regimens than the 28-day regimen. Therefore, the subject is at risk for unscheduled bleeding for a greater period of time which may contribute to potential bias. This potential bias creates some difficulty in comparing rates of unscheduled bleeding between 28 day and 91 day regimens.*
- *A review of NDA 21-544 provides the following data regarding Seasonale (Table 27).*

Table 27 Mean Unscheduled Bleeding and/or Spotting Days Per Subject-Month

Cycle	Seasonique	Seasonale*
1	3.6	3.8
2	2.4	2.9
3	1.8	2.7
4	2.0	2.2

*Seasonale data taken from medical officer's review of NDA 21-544

- *Although the above table represents cross-study data with inherent bias, Seasonique does appear to have numerically less unscheduled bleeding and/or spotting days per subject-month. Seasonique subjects had a mean of 7.8 total days of unscheduled bleeding and/or spotting by Cycle 4 compared to a mean of 8.8 total days for Seasonale (NDA 21-544). The difference in total number of unscheduled bleeding and/or spotting days between these two drug products does not appear to this reviewer to be clinically significant.*

Table 28 illustrates another way to assess the unscheduled (or unanticipated) bleeding and/or spotting that occurs with Seasonique.

Table 28 Analysis of Unscheduled Bleeding/Spotting for Seasonique Subjects, Studies PSE-301 and PSE-302

Days of unanticipated bleeding and/or spotting recorded in the diary per cycle	Cycle 1 % of 829 completers	Cycle 4 % of 486 completers
≤ 6 days	293/829=35%	294/486=60%
≥ 7 days	536/829=65%	192/486=40%
≥ 20 days	242/829=29%	57/486=12%

Source: NDA 21-840, Integrated Summary of Benefits and Risks, Table 6

Medical Reviewer’s Comments

- *Unscheduled bleeding and/or spotting is probably the most important bleeding parameter for patients on oral contraceptives. As shown above in Table 28, “breakthrough bleeding” decreases significantly after one year 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 Seasonique subjects do not raise any safety concerns.*

Table 29 is taken from the medical officer’s review of NDA 21-544 (Seasonale) and serves as another point of comparison to Seasonique.

Table 29 Analysis of Unscheduled Bleeding/Spotting for Seasonale Subjects in NDA 21-544

Days of unanticipated bleeding and/or spotting recorded in the diary per cycle	Cycle 1 % of 385 completers	Cycle 4 % of 261 completers
≤ 6 days	133/385=35%	152/261=58%
≥ 7 days	252/385=65%	109/261=42%
≥ 20 days	136/385=35%	40/261=15%

Source: Adapted from the medical officer’s review of NDA 21-544, Page 54

Medical Reviewer’s Comment

- *As already mentioned, comparing products across studies may be of interest but it is difficult to draw firm evidence-based conclusions on such data. According to the cross-study data, Seasonique may have a lower percentage of unscheduled bleeding and/or spotting lasting ≥ 20 days at the end of Cycle 1. This is difficult to understand since both products are identical for the first 84 days of use. By Cycle 4, Seasonique and Seasonale have similar percentages of subjects with unscheduled bleeding.*

For comparison, Table 30 tracks the same bleeding parameters for Nordette.

Table 30 Analysis of Unscheduled Bleeding/Spotting for Nordette Subjects in PSE 302

Days of unanticipated bleeding and/or spotting recorded in the diary per cycle	Months 1-3 % of 72 completers	Months 10-13 % of 45 completers
≤ 6 days	44/72=61%	27/45=60%
≥ 7 days	28/72=39%	18/45=40%
≥ 20 days	2/72=3%	3/45=7%

Source: NDA 21-840, Integrated Summary of Benefits and Risks, Table 6

Medical Reviewer's Comment

- *The numbers here are too small to draw any comparisons or conclusions.*

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were done.

7.1.6 Less Common Adverse Events

There were no unexpected less common adverse events occurring in the DP3-84/10 treatment arm in either Study PSE-301 or Study PSE-302.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory tests were done at baseline and at the end of the study. Small changes were seen in both treatment groups during the course of up to one year of treatment for all treated subjects. In Study PSE-301, a total of 55 of 681 (8.1%) DP3-84/10 subjects with cholesterol within the normal range at baseline had values above the normal range at end of treatment. Twenty-five subjects (3.7%) had end of treatment cholesterol that went from normal at baseline to below the lower limit of normal. Eighty-seven of 660 subjects (13.2%) who had normal values at baseline for triglycerides had values at the end of treatment that exceeded the upper limit of normal.

Medical Reviewer's Comment

- *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 to the value indicating upper or lower limits of normal. No end of treatment values rose to a clinically significant level.*

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Table 31 Screening and Endpoint Lipid and Hematology Mean Values, Study PSE-301

Test/Treatment Arm	N	Screening Mean	Endpoint Mean	Mean Change from Baseline
Cholesterol				
DP3-84/30	771	180.7 mg/dl	183.4 mg/dl	2.7
DP3-84/10	783	182.0 mg/dl	186.2 mg/dl	4.1
Triglycerides				
DP3-84/30	771	112.4 mg/dl	117.3 mg/dl	4.8
DP3-84/10	783	110.3 mg/dl	119.1 mg/dl	8.8
LDL				
DP3-84/30	767	98.0 mg/dl	103.3 mg/dl	5.3
DP3-84/10	777	99.5 mg/dl	105.9 mg/dl	6.4
HDL				
DP3-84/30	771	60.3 mg/dl	56.7 mg/dl	-3.6
DP3-84/10	781	60.2 mg/dl	56.3 mg/dl	-3.9
Hemoglobin				
DP3-84/30	765	13.7 g/dl	13.8 g/dl	0.1
DP3-84/10	769	13.6 g/dl	13.8 g/dl	0.2
Hematocrit				
DP3-84/30	765	41.6 %	41.6 %	0.0
DP3-84/10	763	41.3 %	41.7 %	0.4

Source: Adapted from NDA 21-840, Clinical Study Report, PSE-301, Page 99

In Study PSE-302, only one of 61 (1.6%) DP3-84/10 subjects with cholesterol within the normal range at baseline had values above the upper limit of normal at the end of treatment. Three of 54 Nordette subjects (5.6%) had cholesterol elevations above the upper limit of normal. Seven of 59 DP3-84/10 subjects (11.9%) who had normal values at baseline for triglycerides had values at the end of treatment that exceeded the upper limits of normal as compared to four of 51 (7.8%) in the Nordette group.

Table 32 Screening and Endpoint Lipid and Hematology Mean Values, Study PSE-302

Test/Treatment Arm	N	Screening Mean	Endpoint Mean	Mean Change from Baseline
Cholesterol				
DP3-84/30	76	184.2 mg/dl	185.3 mg/dl	1.1
DP3-84/10	71	179.5 mg/dl	181.7 mg/dl	2.1
DP3-25/30	62	181.6 mg/dl	183.0 mg/dl	1.4
Nordette	64	181.8 mg/dl	183.2 mg/dl	1.4

Triglycerides				
DP3-84/30	76	105.2 mg/dl	121.2 mg/dl	15.9
DP3-84/10	71	109.2 mg/dl	118.1 mg/dl	8.9
DP3-25/30	62	97.3 mg/dl	111.0 mg/dl	13.6
Nordette	64	115.7 mg/dl	112.5 mg/dl	-3.2
LDL				
DP3-84/30	75	99.3 mg/dl	102.5 mg/dl	3.2
DP3-84/10	69	95.6 mg/dl	99.9 mg/dl	4.4
DP3-25/30	62	101.0 mg/dl	104.0 mg/dl	2.9
Nordette	64	99.7 mg/dl	104.2 mg/dl	4.5
HDL				
DP3-84/30	76	63.8 mg/dl	58.9 mg/dl	-4.9
DP3-84/10	71	61.9 mg/dl	57.1 mg/dl	-4.9
DP3-25/30	62	61.0 mg/dl	56.7 mg/dl	-4.3
Nordette	64	59.1 mg/dl	56.5 mg/dl	-2.6
Hemoglobin				
DP3-84/30	75	13.4 g/dl	13.6 g/dl	0.2
DP3-84/10	69	13.4 g/dl	13.6 g/dl	0.2
DP3-25/30	61	13.4 g/dl	13.4 g/dl	0.1
Nordette	64	13.3 g/dl	13.4 g/dl	0.2
Hematocrit				
DP3-84/30	75	41.1 %	41.5 %	0.4
DP3-84/10	69	40.9 %	41.4 %	0.6
DP3-25/30	61	41.0 %	41.1 %	0.1
Nordette	64	40.4 %	40.6 %	0.2

Source: NDA 21-840, Adapted from Clinical Study Report, PSE-302, Page 106

Medical Reviewer's Comments

- *Although unscheduled bleeding was common in subjects on Seasonique, the effect of this bleeding on hemoglobin and hematocrit values does not appear to be of clinical significance.*
- *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 in all DP3 treatment groups and a small decrease in HDL-cholesterol.*
- *A review of the currently approved Seasonale (NDA 21-544) revealed the following end of treatment mean values for subjects taking Seasonale for four 91-day cycles:*

Test	N	Endpoint Mean
Total cholesterol	264	191.9 mg/dl
Triglycerides	264	128.9 mg/dl
LDL	258	115.3 mg/dl
HDL	263	50.5 mg/dl
Hemoglobin	259	13.7 g/dl
Hematocrit	251	40.8 %

Source: medical officer's review of NDA 21-544

- *The mean changes in serum lipid levels are similar for Seasonale and Seasonique.*

Table 33 Shift Analysis for Liver Function Tests, DP3-84/10 Group (Seasonique), End of Treatment, Study PSE-301

Lab	Baseline	L	%	N	%	H	%	Total
Total Bilirubin (0.2-1.2 mg/dL)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	701	99.3	5	0.7	706
	H	0	0.0	7	43.8	9	56.3	16
	Total	0	0.0	708	98.1	14	1.9	722
ALT (6-37 U/L)	L	0	0.0	1	100	0	0.0	1
	N	1	0.1	685	91.7	61	8.2	747
	H	0	0.0	15	60	10	40.0	25
	Total	1	0.1	701	90.7	71	9.2	773
AST (10-36 U/L)	L	0	0.0	1	100	0	0.0	1
	N	0	0.0	692	94.7	39	5.3	731
	H	0	0.0	18	72.0	7	28.0	25
	Total	0	0.0	711	93.9	46	6.1	757

Source: NDA 28-840, Adapted from Clinical Study Report, PSE-301, Page 107

Table 34 Shift Analysis for Liver Function Tests, DP3-84/10 Group (Seasonique), End of Treatment, Study PSE-302

Lab	Baseline	L	%	N	%	H	%	Total
Total Bilirubin (0.2-1.2 mg/dL)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	62	100	0	0.0	62
	H	0	0.0	1	50	1	50.0	2
	Total	0	0.0	63	98.4	1	1.6	64
ALT (6-37 U/L)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	62	93.9	4	6.1	66
	H	0	0.0	4	100	0	0.0	4
	Total	0	0.0	66	94.3	4	5.7	70
AST (10-36 U/L)	L	0	0.0	0	0.0	0	0.0	0
	N	0	0.0	64	95.5	3	4.5	67

	H	0	0.0	3	100	0	0.0	4
	Total	0	0.0	67	95.7	3	4.3	71

Source: NDA 28-840, Adapted from Clinical Study Report, PSE-302, Page 122

Medical Reviewer's Comments

- *Review of the above data shows that 6.1% and 4.5% of subjects who had normal ALT and AST at baseline ended the study with elevated values. Review of the Seasonale data showed the corresponding percentages to be similar at 4.0% and 3.1%.*
- *Small increases in serum ALT, AST, and bilirubin concentrations are known effects of treatment with combined oral contraceptives.*

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*

Not applicable.

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

See Tables 33 and 34.

7.1.7.3.3 *Marked outliers and dropouts for laboratory abnormalities*

Not applicable.

7.1.7.4 Additional analyses and explorations

No additional analyses and explorations were done.

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7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

There were no notable changes in vital signs (blood pressure, heart rate, weight or temperature) over time within or between the treatment groups.

Table 35 Vital Signs, Mean Change from Baseline, Safety Cohort (All Treated Subjects)

	Mean Change From Baseline
Systolic Blood Pressure (mmHg)	
DP3-84/30	1.5
DP3-84/10	1.7
DP3-25/30	2.1
Nordette	3.5
Diastolic Blood Pressure (mmHg)	
DP3-84/30	0.7
DP3-84/10	0.6
DP3-25/30	-1.9
Nordette	-0.6
Weight Gain (lbs)	
DP3-84/30	2.2
DP3-84/10	2.6
DP3-25/30	2.3
Nordette	1.3

Source: NDA 21-840, Adapted from the Integrated Summary of Safety, Page 20

Medical Reviewer's Comments

- *There were no notable changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, weight or temperature) over time within or between the treatment groups.*
- *Weight gain does not appear to be a significant problem with Seasonique.*

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.8.3 Standard analyses and explorations of vital signs data

See Table 35.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

No additional analyses and explorations were done

7.1.9 Electrocardiograms (ECGs)

Not applicable.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.3.1 *Analyses focused on measures of central tendency*

Not applicable.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

Not applicable.

7.1.9.3.3 *Marked outliers and dropouts for ECG abnormalities*

Not applicable.

7.1.9.4 Additional analyses and explorations

Not applicable.

Endometrial Biopsy Findings

Endometrial biopsy data was only obtained in Study PSE-302. Subjects randomized to DP3-84/30 and DP3-84/10 were divided into two groups in this study. Group 1 was to undergo their end of study endometrial biopsy between days 60 and 84 of their last treatment cycle. Group 2 was to undergo their end of study endometrial biopsy between days 89 and 91 of their last treatment cycle. Subjects randomized to DP3-25/30 were to undergo their end of study endometrial biopsy between days 26 and 28 of their last treatment cycle, while subjects

randomized to Nordette were to undergo their end of study endometrial biopsy between days 11 and 21 of their last treatment cycle. Three blinded reviewers examined and classified each biopsy.

No exclusionary criteria (i.e., hyperplastic or malignant endometrial changes or other significant endometrial pathology) were found in any of the pre-therapy biopsies.

Table 36 Disposition of Treated Subjects Who Underwent Endometrial Biopsies

	DP3-84/30 (N=95) N	DP3-84/10 (N=95) N	DP3-25/30 (N=89) N	Nordette (N=93) N	Total (N=372) N
Safety Cohort	95	95	89	93	372
Pre-Treatment Biopsy	94	95	89	92	370
Last Cycle Biopsy	55	63	50	58	226
Both Biopsies Done	55	63	49	57	224

Source: NDA 21-840, Integrated Summary of Safety, Page 74

Table 37 Distribution of End of Treatment Endometrial Biopsy Results

	DP3-84/30 (N=161)		DP3-84/10 (N=181)		Nordette (N=169)	
	N	%	N	%	N	%
No endometrium	9	5.6	24	13.3	4	2.4
Insufficient tissue	8	5.0	8	4.4	11	6.5
Inactive	69	42.9	76	42.0	81	47.9
Atrophic	14	8.7	14	7.7	7	4.1
Menstrual	16	9.9	14	7.7	9	5.3
Proliferative	18	11.2	29	16.0	21	12.4
Secretory	27	16.8	16	8.8	36	21.3
Hyperplastic	0	0.0	0	0.0	0	0.0

Source: NDA 21-840, Integrated Summary of Safety, Page 76

Medical Reviewer's Comments

- *No cases of endometrial hyperplasia or worse were diagnosed in Study PSE-302. Biopsy results demonstrated that the two 91-day extended regimen DP3-84/30 and DP3-84/10 treatments do not promote any unexpected changes in the endometrium either during the course of active combination treatment or during the ethinyl estradiol monotherapy period, at either the 30 mcg or 10 mcg ethinyl estradiol monotherapy dose.*
- *There were no obvious safety concerns from the endometrial biopsy evaluations.*

Hormonal-Related Symptoms

Medical Reviewer's Comments

- *The study of hormone-related symptoms was not incorporated into the study design for either study (PSE-301 or PSE-302) submitted in this NDA thus these hormone-related symptoms were not studied in an adequate and well-controlled manner. Treated subjects were not required to qualify for entry into the study based on any minimum severity criterion for any particular hormone-related symptom or symptoms. The Applicant merely had each subject record daily in an electronic diary, the existence and severity of acne, headache, fatigue, bloatedness, breast tenderness, swelling in hands/ankles, migraine headache, cramps/pelvic pain, muscle/joint pain, and back pain. In addition, the existence and severity of feelings or a mood of: depression/hopelessness, anxious/tenseness, sadness/tearfulness, or anger/irritability were to be recorded on a VAS scale by the subject in the daily electronic diary.*
- *The Applicant submitted with this NDA a list of graphs which tracked each of the above symptoms through treatment, based on the information obtained in the daily diaries. Each graph illustrated the percentage of all treated subjects (Safety cohort) reporting a particular symptom. The Applicant concluded that no consistent systematic changes in any of these hormone-related symptoms were observed through treatment. However, a slight trend toward reduction in reported acne of any severity was seen for DP3-84/10. A slight trend favoring a reduction in reported breast tenderness, through the first 91-day cycle and then remaining constant, was also noticed for DP3-84/10.*
- *In summary, the improvement in hormonal-related symptoms with Seasonique was not studied as an endpoint in this NDA but studied only subjectively as described above. The Applicant concludes that "results need to be further explored".*

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not applicable.

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7.1.12 Special Safety Studies

Not applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable.

7.1.14 Human Reproduction and Pregnancy Data

Not applicable.

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

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

7.1.17 Postmarketing Experience

Not applicable.

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

See Table 16

7.2.1.1 Study type and design/patient enumeration

See table 1

7.2.1.2 Demographics

See Tables 3 and 11.

7.2.1.3 Extent of exposure (dose/duration)

See Table 16

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary clinical sources were used to evaluate safety.

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

Not applicable.

7.2.2.4 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the study drug for an adequate duration of time.

7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Adequacy of Routine Clinical Testing

Not applicable.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Not applicable.

7.2.7 Assessment of Quality and Completeness of Data

The data provided in the submission is complete.

7.2.8 Additional Submissions, Including Safety Update

Not applicable.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following points summarize the safety findings and limitations of data:

- The combination of the primary study PSE-301 and the supportive study PSE-302 provides enough subject exposure to assess safety for Seasonique.
- The primary adverse event related to Seasonique is unanticipated bleeding and/or spotting. Across both studies, 6.3% of subjects discontinued, at least in part, due to bleeding and/or spotting. Although this side effect diminishes somewhat with use, 12% of 486 subjects still had over 20 days of unanticipated bleeding/spotting in the fourth 91-day cycle of use and 40% had greater than seven days of unanticipated bleeding/spotting in the fourth cycle.
- Despite the prolonged number of days of unanticipated bleeding/spotting it appears that the quantity of blood loss with this bleeding is usually minimal. There was no evidence in the hematology laboratory dataset from the pivotal PSE-301 trial that there are significant problems with anemia in those subjects taking Seasonique. Mean hematocrit and hemoglobin values remained stable during the study.
- There were no notable changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, weight or temperature) over time within or between the treatment groups.
- From the data reviewed, Seasonique appears safe to use for pregnancy prevention.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

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7.4.2 Explorations for Predictive Factors

Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable.

7.4.2.3 Explorations for drug-demographic interactions

The product is intended for reproductive age women. The pharmacologic class is well characterized. There are no separate race or ethnicity considerations in regard to safety or efficacy.

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The key issue in this NDA is the risk and benefit profile of Seasonique and whether the substitution of seven days of 0.01 mg of ethinyl estradiol monotherapy for placebo every 84 days influences approval.

8.2 Drug-Drug Interactions

Not applicable.

8.3 Special Populations

This product is only recommended for use in women of childbearing age.

8.4 Pediatrics

A separate pediatric program is not required. Combination oral contraceptives are safe and effective in postpubertal females. This product is not intended for pre-pubertal use.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

Standard post-marketing surveillance (AERS) is recommended to further monitor the efficacy and safety of Seasonique.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Based on the trial data submitted, Seasonique appears to be safe and effective for the indication of prevention of pregnancy. The Pearl Index is 1.77 as determined by the medical reviewer and FDA statistician and no serious safety concerns were demonstrated in the clinical studies. In addition, the total doses of both the levonorgestrel and ethinyl estradiol contained in this drug are within the range of currently approved oral contraceptives.

The Applicant has not addressed (through head to head clinical trials) the benefit of the substitution of ethinyl estradiol 0.01 mg for the placebo tablets found in the already approved Seasonale formulation. Cross-study analysis does indicate however that the bleeding profile of Seasonique may be somewhat better than Seasonale.

Seasonique is not a “me too” drug. It has no placebo tablets as is found in all other oral contraceptives. Rather, the formulation is innovative with theoretical (not yet proven) benefits of increased cycle control, relief from hormone withdrawal symptoms, and possibly better ovulation suppression. This is not just a “me too” case of adding more estrogen to the already hormonally active tablets but actually the addition of 0.07 mg ethinyl estradiol at the end of each active cycle.

The Applicant is seeking prevention of pregnancy as an indication for therapy. For this indication, the Applicant has complied with this Division’s recommendations for obtaining approval for a new oral contraceptive and has demonstrated safety and efficacy, without apparent safety concerns, in a somewhat novel dosage form. The small amount of estrogen substituted for placebo may (or may not) represent an improvement in oral contraceptive

technology but it does represent a new unique approach to oral contraception while also being safe and effective.

This reviewer recommends approval of Seasonique. However, approval should be contingent on agreements with the Applicant concerning product labeling.

9.2 Recommendation on Regulatory Action

Approval of Seasonique™ for prevention of pregnancy is recommended based on the Applicant's demonstration of an acceptable Pearl Index and an acceptable safety profile. Approval is contingent on agreements with the Applicant concerning product labeling.

9.3 Recommendation on Postmarketing Actions

Standard post-marketing surveillance (AERS) is recommended to further monitor the safety of Seasonique.

9.3.1 Risk Management Activity

No specific risk management steps are warranted based on presently available data.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

At this time, labeling for this drug product has not been finalized.

9.5 Comments to Applicant

10 APPENDIX

10.1.1.1 Section 1: Combination Oral Contraceptives containing Ethinyl Estradiol/Levonorgestrel Approved in the United States

NDA #	Proprietary Name/ Applicant	Approval Date	EE strength (mg)	LNG strength (mg)	Generic/ #/Applicant/year
016672/ 016806	Ovral Ovral-28 Wyeth Ayerst	1968	0.05	0.25*	Ogestrel 075406 SCS/1999
017612/ 017802	Lo/Ovral Lo/Ovral-28 Wyeth Ayerst	1976	0.03	0.15**	Low-Ogestrel-21/28 075288 Watson/1999 Cryselle 075480 Duramed Pharm Barr/2001
018668/ 018782	Nordette-21 Nordette-28 Wyeth Ayerst	5/10/82	0.03	0.15	Portia-21 075866 Barr Labs/2002 Levora -21/28 073592/ 073594 Watson/1993
019192/ 019190	Triphasil 21 Triphasil 28 Wyeth Ayerst	11/01/84	0.03 0.04 0.03	0.05 0.125 0.075	Trivora-21/28 074538 Watson/1997 Enpresse-21/28 075809 Duramed Pharm Barr/2001
020683	Alesse 21 Alesse 28 Wyeth Ayerst	3/27/97	0.02	0.1	Lessina-21/28 075803 Barr/2002 Aviane-21/28 075796 Duramed Pharm Barr/2001
020860	Levlite Berlex	7/13/98	0.02	0.1	
020946	Preven Gynetics	9/01/98	0.05	0.25	
021544	Seasonale Barr Labs	9/05/03	0.03	0.15	

Source: NDA 21-840, Integrated Summary of Benefits and Risks, Adapted from Table 1, Page 1

(*) Ovral (and its generic equivalent, Ogestrel 0.5/50) contains 0.5 mg d,l-norgestrel of which 0.25 mg is the active progestin levonorgestrel.

(**) Lo/Ovral (and its generic equivalents, Low-Ogestrel and Cryselle) contains 0.3 mg d,l- norgestrel, of which 0.15 mg is the active progestin levonorgestrel.

10.2 Review of Individual Study Reports

Not applicable.

10.3 Line-by-Line Labeling Review

At this time, labeling for this drug product has not been finalized.

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this page is the manifestation of the electronic signature.**

/s/

Ronald Orleans
8/16/2005 06:21:45 PM
MEDICAL OFFICER

Shelley Slaughter
8/17/2005 12:52:43 PM
MEDICAL OFFICER

I have read the objective data and the Medical
Officer's comments and discussion presented in this review.
I do not concur with the conclusion and
regulatory recommendation. See Group Leader Memorandum date August
17, 2005.

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