- Additional endometrial histology sub-study ---prohibited treatment added
- Subjects will receive home urine pregnancy test kits to check for pregnancy during pill packs in which there are no scheduled visits
- CRSS antidepressants/anxiolytic exclusion has changed to prohibit these medications only during the first 84 days of test article use
- Relevant family history was added to the protocol
- Subjects who withdraw from the study early, who are 40 or older and have not had a mammogram in the past six months must have a mammogram at the early termination visit.

On April 25, 2003 Wyeth received a correspondence from FDA clarifying the request fro the April 2002 teleconference. This correspondence stated FDA no longer required an extension study for long-term safety and bleeding patterns. FDA requested that Wyeth assess return to menses and fertility in subjects that have been treated with LNG 90µg/EE 20µg continuous use regimen for at least one year.

On August 18, 2003 Wyeth submitted a protocol **entitled "A Phase 3 Multi-Center Study to** Evaluate the Return to Spontaneous Menses for Subjects Receiving Prior Treatment with a Continuous Daily Regimen of Levonorgestrel and Ethinyl Estradiol for Oral Contraception (Protocol #314-NA).

On September 12, 2003 Wyeth submitted a protocol **entitled "Multiple Dose Study for the** Pharmacokinetics of Levonorgestrel (90µg and Ethinyl Estradiol (20µg) Administered Orally to Healthy Women (Protocol 106-US).

On September 30, Wyeth submitted a change to the Phase 3 protocol. A pulse rate measurement at the standing position was added to the vital signs procedures at screening, on days -1, 13, 27, and at the final evaluation.

Between November 5, 2003 and April 21, 2004 there were 4 correspondences between Wyeth and FDA regarding Chemistry issues.

On May 6, 2004 Wyeth submitted their first proprietary name for review.

On May 27, 2004 in correspondence between Wyeth and FDA the Division agreed that preclinical study reports do not have to be included with the NDA submission. A comprehensive summary of the non-clinical data should be included with references to where certain reports were previously submitted.

On July 28 in a correspondence Wyeth submitted the following changes to their Phase 3 protocol:

- Changes to the Medical Monitor and Clinical Scientists
- Incorporation of region specific changes, changes specific to endometrial histology sub-study, and Canadian one-year extension study

- **"Approximately" has been added to the num**ber of subjects to allow for flexibility
- The number of subjects expected to complete the 3-month sub-study (assuming a 3-month 20% dropout rate) is changed from 165 to 246 (typographical error)
- The definition of return to spontaneous menses was incorporated as stated in study protocol
- Information regarding pregnancies has been enhanced to incorporate the Canadian one-year extension study

On August 6, 2004 Wyeth submits additional changes to Protocol 314, including:

- Medical monitor and emergency contacts changed
- Revisions of the synopsis, concomitant treatment changed to be consistent with the Phase 3 protocol (313-NA)
- Revising the protocol, concomitant treatment, and permitted treatment to be consistent with Phase 3 protocol

On September 7, 2004 Wyeth received a letter from FDA requesting a new proposed proprietary name be submitted due to potential confusion between the submitted name and names of marketed products.

On September 10, 2004 Wyeth requested a Pre-NDA meeting

On September 27, 2004 FDA confirmed a November 22, 2004 Pre-NDA meeting

On October 7, 2004 two additional correspondence Chemistry issues are discussed

On November 1, 2004 Wyeth accepts FDA responses faxed on October 19, 2004 regarding the single unit dispenser. b(4)

On November 8, 2004 Wyeth submits a statistical analysis plan for Study 0858A2-313-NA to FDA as an information amendment. No discussions between Wyeth and the Division on this analysis plan were held. The protocol was never amended to incorporate the statistical analysis plan.

On November 10, 2004 the Pre-NDA meeting sche**duled for November 22 is cancelled at FDA's** request. The Division felt that there were no major program-related issues that warranted a Pre-NDA meeting b(4)

On November 16 through December 7, 2004 CMC issues continue to be discussed.

On May 27, 2005 Lybrel™ was submitted by Wyeth (NDA 21-864).

Appears This Way
On Original

2.6 Other Relevant Background Information

Refer back to correspondence dates April 8, 2004 and November 8 regarding sub-studies and potential indications other than contraception

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Initial deficiencies identified by the FDA reviewing chemist are not satisfactorily resolved by the sponsor at this time

3.2 Animal Pharmacology/Toxicology

There are no significant review issues with Pharmacology/Toxicology or Microbiology.

3.3 Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications (DDMAC) submitted their labeling review. DDMAC has objections to the proprietary names of Lybrel and —— from a promotional perspective. b(4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The sponsor presents an integrated summary of efficacy and safety that has pooled data from studies 0858A2-313-NA and 0858A2-315EU.

Reviewer's Comment
No prior discussions were held with Wyeth that discussed any study other than Study 0858A-313-NA as the primary "proof-of-efficacy" study.

The primary focus for the review of efficacy will be study 0858A2-313-NA and it will be reviewed in detail. Study 0858A2-315EU will also be reviewed in lesser detail relating to pregnancy rates, discontinuation rate and comparative bleeding.

4.1 Sources of Clinical Data

Submission of this NDA is via eCTD on May 27, 2005. This submission is based on a Phase 1 study (106-US) to determine the pharmacokinetic properties of LNG and EE, a Phase 2 study

(208-US) to demonstrate the inhibition of ovulation, and 2 pivotal Phase 3 safety and efficacy studies (313-NA and 315-EU).

4.2 Tables of Clinical Studies

Table 1 Sponsor's Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	106-US	5.3.3.1 CSR-55147 Study 106	PK profiles of LNG and EE	Open-label	Tablet, LNG 90 µg/EE 20 µg, oral, daily	18	Healthy subjects	28 days	Complete; Full
PD	208-US	5.3.5.2 CSR-50115 Study 208	Inhibition of ovulation	Open-label	Tablet, LNG 90 µg/EE 20 µg, oral, daily	58	Healthy subjects	84 days	Complete; Full
Efficacy	313-NA	5.3.5.2 CSR-55064 Study 313	Long-term; Efficacy and Safety	Open-label	Tablet, LNG 90 µg/EE 20 µg, oral, daily	2134	Healthy subjects	1 year	Complete; Full
Efficacy	315-EU	5.3.5.1 CSR-55078 Study 315	Long-term; Efficacy and Safety	Open-label active-controlled	Tablet, LNG 90 µg/EE 20 µg, oral, daily	641 (323 test drug, 318 active control)	Healthy subjects	1 year	Complete; Full

EE = ethinyl estradiol; LNG = levonorgestrel; PD = pharmacodynamic; PK = pharmacokinetic.

4.3 Review Strategy

This review was conducted utilizing the following strategy:

- Overview of total clinical documents with emphasis on study 0858A2-313NA. The pregnancy rate (including analyses of the Pearl index and Life table analyses) will be done. In addition the effect of the high discontinuation rate will be explored and what effect discontinuations related to bleeding may have had on the overall utility of this product. Efficacy data relating to study 0858A2-315 will be presented in the appendix of the review and will be referred to as Study 2 (0858A2-315)
- Review of the total electronic submission
- Review of pertinent Case Report Forms (CRFs)

4.4 Data Quality and Integrity

- Review will be based on possible bias relating to financial ties
- Reviewing source documentation for efficacy analysis
- Spot checking database for inconsistencies

4.5 Compliance with Good Clinical Practices

The study protocols and amendments were reviewed by the appropriate Institutional Review Boards (IRBs). Informed consent was obtained according to the ethical principles states in the latest version of the Declaration of Helsinki (Republic of South Africa; 1996) and the applicable guidelines for Good Clinical Practice.

4.6 Financial Disclosures

The sponsor appears to have adequately disclosed financial arrangements with the clinical investigators as recommended by the FDA guidance for industry on Financial Disclosure by Clinical Investigators.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The sponsor performed two 2 pharmacokinetic studies (Studies 0858A2-106US and 0858A2-208-US).

Study protocol 0858A2-106US was a multiple dose study of the pharmacokinetics of LNG 90μg and EE 20μg. It enrolled 18 healthy subjects who were given oral doses for 28 days. A full pharmacokinetic profile was obtained on days 1, 14, and 28 and a model-independent pharmacokinetic analysis was performed. Additionally, the effects of sex hormone binding globulin (SHBG) on the pharmacokinetics of LNG were examined.

Following multiple doses of LNG 90μg and EE 20μg the accumulation factor of LNG predicted a 2.7 fold increase in exposure as compared with a single dose. Since the t½ of LNG is approximately 35 hours, it is expected to accumulate in plasma when administered every 24 hours. LNG appears to reach steady state by day 12. The mean C_{max} increased by 123% on days 14 and 28, respectively, as compared to day 1. The mean AUC over 24 hours increased by 315% and 353% on days 14 and 28, respectively.

LNG is >99% protein bound, primarily to SHBG. Synthesis of SHBG is inducible by EE. An increase of approximately 100% in SHBG concentrations was observed in this study with multiple doses of LNG 90μg and EE 20μg. This increase in SHBG was accompanied by a 30% decrease in unbound LNG in plasma with multiple doses of LNG 90μg and EE 20μg. The mean plasma concentration of unbound LNG was higher on day 28 than on day 1, indicating accumulation of unbound LNG in plasma with multiple dosing. The mean C_{max} and AUC increased by 68% and 217% respectively on day 28 as compared to day 1.

Following multiple dosing every 24 hours, EE with a mean $t_{½}$ of approximately 20 hours, shows a 1.8 fold increase in exposure. Although it may not be significant, there is proportional increase in EE and SHBG concentrations. The EE levels reach steady state by day 12. The pharmacokinetics of EE was essentially similar on the 2 days of multiple dose measurements (days 14 and 28). The mean C_{max} increased by 52% and 56% in days 14 and 28, respectively, as compared to day 1. Similarly, the AUCs over 24 hours increased by 84% and 90% on days 14 and 28, respectively, compared to day 1.

Study 0858A2-208-US was a single center, open-labeled study with a single treatment group. Fifty-eight (58) women under the age of 36 were studied to determine the ability of a continuous

use regimen of monophasic LNG 90μg and EE 20μg to inhibit ovulation over 84 days of therapy.

During treatment in the valid for efficacy population, no subject had an on-therapy follicle diameter > 10mm with an on therapy progesterone > 6.36nmol/L within 10 days. During all 3 pill pack segments at least 90% of the valid for efficacy subjects had a Hoogland and Skouby score grade 0, 1, or 2 (no activity, potential activity, non active follicle-like structure, respectively). No subject was characterized as grade 4 (luteinized unruptured follicle) or grade 5 (ovulation). Therefore, ovulation was judged to have been inhibited in all 37 women in the valid for efficacy population. During treatment in the ITT population, ovulation was judged to have been inhibited in all 58 women. The mean (±SD) time to return to ovulation after cessation of treatment was 15.6 (±4.8) days in the valid for efficacy population and 16.5 (±8.5) days in the ITT population.

5.2 Pharmacodynamics

No special pharmacodynamic studies were performed with LNG 90μg and EE 20μg continuous regimen.

5.3 Exposure-Response Relationships

The exposure response relationship of LNG 100μg and EE 20μg has been well-documented in the approval of the sponsor's Alesse product® (approved 1997). The primary differences between Alesse® and Lybrel LNG 90μg and EE 20μg are the fact that Lybrel has 10μg ***less*** per day of LNG and will be given continuously without any withdrawal of hormone which had been the usual treatment regimen. In the pK studies Lybrel appeared to inhibit ovulation over a 3-month period. Wyeth has insisted over past 30 plus years that the ratio of LNG:EE of 5:1 was paramount for effective stabilization of the endometrium and lessening of overall bleeding compared to other E+P combinations. By decreasing the LNG by 10 μg per day, but supplying the product continuously, it is expected that the endometrium will be stabilized and periods of amenorrhea will be enhanced.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Lybrel™ is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

6.1.1 Methods

The general method used in reviewing efficacy for an oral contraceptive includes:

- Confirm the number of pregnancies "on treatment", the on-treatment pregnancies plus those with an estimated dates of conception within 7 days after treatment, and the on-

treatment pregnancies pus those with estimated dated of conception within 14 days after **treatment. This reviewer will compute all pregnancies that occurred within the Agency's definition of "on treatment" pregnancies** (all pregnancies within 14 days of the last active combination drug product).

- Confirm that cycle information provided by the sponsor is accurate and utilizes appropriate age of the subjects.
- **Verify the sponsor's mathematical calculation of the Pearl's index and integrate that with that of the Division's statistician.**

6.1.2 General Discussion of Endpoints

The primary endpoint for the evaluation of all oral contraceptives has traditionally been the Pearl **index. The Pearl index was defined as "pregnancies per 100 woman-years of use," and was** computed by dividing the number of on-treatment pregnancies by the number of woman-cycles (or 28 day intervals) of observation, then multiplying by 1300. The Pearl index was treated as a proportion, and 2-sided 95% confidence intervals (CI) were computed for overall values as well as method and user failures.

The denominator for the Pearl Index was to include all pill packs ***except*** for those in which:

1. Backup contraception was used (or unknown);
2. Three (3) or more consecutive days of pill were missed, either
   - During current pill pack, or
   - The missed consecutive days spanned the previous pill pack into the current pill pack, ending in current pill pack (current pill pack was to be excluded), or
   - What should have been the start of study drug of the first pill pack only if he subject started taking her first pill on day 4 or later from the start of her menses;
3. Five (5) or more total days of pills were missed in any pill pack;
4. Prohibited medication was taken within a time frame that could affect contraceptive efficacy;
5. The subject was not sexually active (or unknown); or
6. For subjects who became pregnant, any pill pack that began after the EDC.

Another method of evaluating efficacy pregnancy in pregnancy prevention is the use of the Life table pregnancy rate. For the Life table pregnancy rate, pregnancy over time is described by treating each cycle (or 28-day interval) of use individually. The pregnancy rate was computed for each specific 28-day interval of use as well as cumulatively from the first 28-day interval to each subsequent 28-day interval, by calculation of the conditional probabilities of becoming pregnant or continuing use. Life tables for each treatment group were produced with the overall (method plus user) pregnancy rate, as well as separately for each component.

The primary safety endpoints are the number of subjects who discontinue within the first year because of an adverse event that will not allow the subject to continue using this method of contraception.

6.1.3 Study Design

The sponsor performed two Phase 3 studies designed to support the safety and efficacy of Lybrel®. Study 313-NA was intended to support registration of the drug product in the US while study 315-EU was intended to support registration in Europe. Study 313-NA is a multicenter, open-label study designed to demonstrate the safety and contraceptive efficacy of an oral contraceptive containing a combination of LNG 90µg/EE 20µg in a continuous-use regime, dispensed as 28-day pill packs. Study 313-NA comprised a single treatment group and was conducted at 84 centers in the US and 8 centers in Canada to monitor the efficacy and safety of the continuous use LNG 90µg/EE 20µg regimen.

This study also included 2 sub-studies. The sub-study entitled the cycle-related symptom sub-study (CRSS) will be reviewed even through the sponsor elected not to seek a claim regarding symptoms and an endometrial histology sub-study will be reviewed.

A total of 2,134 subjects received study drug. Each subject was to participate in the study for approximately 13 months (up to 15 months for subjects who participated in the CRSS).

Study 315-EU was a randomized, multicenter, open-labeled study conducted in 39 centers in Europe to evaluate the safety and efficacy of the continuous-use LNG 90µg/EE 20µg regimen (dispensed as 28-day pill packs) as well as a 21-day cyclic regimen of LNG 100µg/EE 20µg, which was followed by a 7-day hormone-free interval. This study was designed to support registration of this product in Europe. This study was not presented during the pre-NDA stage as **a "proof of efficacy" study for US registration.** This study included a metabolic sub- study.

A total of 641 subjects received study drug. Each subject was to participate in the study for approximately 13 months (15 months for subjects requiring a washout period for the metabolic sub-study).

6.1.4 Efficacy Findings

Study 313-NA was initiated in February 2003 and was completed in September 2004.The primary objective of Study 313-NA was to evaluate the safety and contraceptive efficacy of an OC containing a combination of LNG 90µg/EE 20µg in a continuous regimen. The secondary objectives of this study were to evaluate the effects of the LNG 90µg/EE 20µg continuous-use regimen on vaginal bleeding, endometrial histology, hemostais measures, hemoglobin levels, discontinuation rates, subject satisfaction, and cycle-related symptoms and work productivity in subjects with these symptoms at baseline.

Subjects were to be enrolled at approximately 80 sites in North America; approximately 22 of the sites were to enroll subjects for the CRSS and approximately 5 were to enroll subjects for the endometrial histology sub study. For each site, no more than approximately 20% of subjects were to be older than 35 years at the time of enrollment. Each subject was to participate in the study for approximately 13 months. Study procedures that were required for all subjects in the

total population were also required for subjects in each sub-study; however, additional procedures specific to each sub-study were performed.

The following flow-chart (Table 6.1-1) are assessments that were required for all the study subjects will be shown on this page and the following page:

Table 2 Sponsor's Table 6.1-1

Table 6.1-1: Study Flowchart

	Pretreatment		Treatment Interval							Posttreatment
Visit	1A[a]	1B[a,b]	2			3		4		5[c]
Days	5-18	12-26	1-56	57-84	85-168	169-196	197-252	253-280	281-364	1-15
Pill Packs			1, 2	3	4, 5, 6	7	8, 9	10	11, 12, 13[d]	
Informed consent/history	X									
Inclusion/exclusion criteria	X	X								
Physical and gynecologic examination	X					X				X
Mammogram (if needed)[e]	X									X
Body weight/sitting blood pressure	X	X		X		X		X		X
Laboratory safety screen	X					X				X[f]
Chlamydia screening test[g]	X									
Serum β-hCG[h]	X									X
Urine pregnancy test[h]		X	X	X	X	X	X	X	X	
Cervical cytology smear	X					X				X[i]
Dispense home urine pregnancy test kit[j]		2		3		2		3		
Dispense adverse event diary[k]	1									
Dispense diaries		3		4		3		3[l]		
Dispense pill packs		3		4		3		3		
Collect adverse event diary[m]				1						
Collect diaries				2		4		3		4
Collect pill packs				2		4		3		4
Assess tobacco use and sexual activity	X	X		X		X		X[n]		X
Subject satisfaction questionnaire	X			X		X		X		X
Assess adverse events	X----									----X
Phone call			X[o]							

Note: Subjects in the study were to take 1 pill daily for 1 year. Subjects who did not qualify for the cycle-related symptom substudy could continue to participate as a subject in the total population if they met all other criteria.

a. Visit 1A and 1B were to occur within the same cycle.
b. Results from visit 1A testing must have been available by visit 1B.
c. Visit 5 was to occur between days 1 and 15 after day 364 or the last dose of study drug. Any remaining pill packs and diaries were to be returned to the site at this visit.
d. For subjects interested in participating in the 1-year extension study (0858A2-320-CA), the tests and procedures performed during pill pack 13 (days 337 to

Table 6.1-1: Study Flowchart

	Pretreatment		Treatment Interval							Posttreatment
Visit	1A[a]	1B[a,b]	2			3		4		5
Days	5-18	12-26	1-56	57-84	85-168	169-196	197-252	253-280	281-364	1-15
Pill Packs			1, 2	3	4, 5, 6	7	8, 9	10	11, 12, 13[d]	

354; visit 4A) served as the screening tests and procedures at visit 5. This visit was to be a transition period into the 1-year extension study 0858A2-320-CA.

e. A mammogram was required for subjects who were aged 40 years or older at visit 1A or who would turn 40 during the course of the study. A mammogram within 6 months before visit 1A was acceptable for these subjects if a copy of the report was obtained and results were recorded on the case report form. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the mammogram did not need to be repeated at visit 5 if it had been performed at visit 1A in this study.
f. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the laboratory safety screen did not need to be repeated at visit 5 if it had been done at visit 1A in this study.
g. A chlamydia test was required for subjects aged 25 years or younger and other subjects who had risk factors for chlamydia, as determined by the investigator at visit 1A. If results were positive, the investigator was to provide the subject with the appropriate treatment. A positive test result did not preclude the subject from participating in the study.
h. A serum β-hCG pregnancy test was required at visit 1A and the final visit. A urine pregnancy test was to be performed at all other visits and as indicated to exclude pregnancy.
i. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the cervical cytology smear did not need to be repeated at visit 5 if it had been done at visit 1A.
j. Subjects were instructed to use the home urine pregnancy test kit to check for pregnancy during pill packs in which there were no scheduled visits.
k. One (1) diary card was to be dispensed at visit 1A for the assessment of adverse events (symptoms and complaints).
l. For subjects who were transitioning into the 1-year extension study 0858A2-320-CA, diaries for pill packs 11 and 12 and if applicable for pill pack 13 were dispensed. For those subjects given a diary for pill pack 13, the white ply was to be returned to the study site in a prepaid envelope.
m. The adverse event diary card dispensed at visit 1A was to be collected at visit 2.
n. Posttreatment contraception was to be discussed with all subjects. Participation in the 1-year extension study 0858A2-320-CA was to be discussed with subjects at the Canadian sites.
o. A phone call was to be made during the first pill pack (days 1 to 28) to review proper pill use (ie, check compliance).

Study 313-NA was conducted in the following manner:

Pretreatment
Days 5 to 18 (Visit 1A)
Study and/or study personnel were to complete the following procedures during visit 1A (days 5 to 18)

1. Signed and dated written informed consent form,
2. A complete medical history and relevant family history,
3. Verification of inclusion/exclusion criteria,
4. A complete physical examination (including body weight, sitting blood pressure, height, and neurologic examination,
5. Gynecologic examination (including breast examination and rectovaginal examination),
6. A mammogram was required for subjects who were 40 years or older at visit 1A or who would turn 40 during the course of the study. A mammogram within 6 months before visit 1A was acceptable for these subjects if a copy of the report was obtained and results were recorded on the CRF,
7. Laboratory safety screen (including urinalysis, hematology, and blood chemistry),
8. Chlamydia screening test for subjects who were 25 years old or younger and other subjects who had risk factors for Chlamydia, as determined by the investigator. If the results were positive, the investigator was to provide the subject with the **appropriate treatment. A positive test did not preclude subject's participation in** the study,
9. Serum ß-human chorionic gonadotropin (ß-hCG) pregnancy test,
10. Cervical cytology smear,
11. Dispensing of adverse event diary card for the assessment of adverse events (symptoms and complaints),
12. Subject satisfaction questionnaire,
13. Assessment of tobacco use, sexual activity , and risk of pregnancy,

The following additional procedures were required for subjects in the CRSS (not reviewed in this review cycle)

14. Dispensing of 1 cycle-related symptom questionnaire (i.e. 17-item Penn DSR) and 4 work productivity questionnaires (i.e. Endicott Work Productivity Scale [EWPS] to pre-qualified subjects,

The following additional procedures were required for subjects in the endometrial histology sub study:

15. A urine pregnancy test, which must have had a negative result before the endometrial biopsy was performed,
16. Endometrial biopsy, performed after collection of blood and urine samples, and a cervical cytology smear.

Days 12 to 26 (Visit 1B)
Subjects and/or study personnel were to complete the following procedures during visit 1B (days 12 to 26)

1. Verification of inclusion/exclusion criteria,
2. Body weight and sitting blood pressure,
3. Urine pregnancy test,
4. Dispensing of 2 home urine pregnancy test kits (to be used when the subject considers it important). Subjects who had a positive test result were instructed to call the site, stop taking study drug, use a back-up method of birth control, and immediately visit the site for a serum pregnancy test to confirm the positive result.
5. ***Dispensing of 3 diaries. Diary cards were to be retained as source documents.***
6. ***Dispensing of 3 pill packs.***
7. Assessment of tobacco use, sexual activity, and risk for pregnancy.
8. Assessment of adverse events.

Subjects in the CRSS underwent the following additional procedures:

9. Verification of qualification for the CRSS. If the subject did not volunteer or receive money for work, she was not to complete the additional work productivity questionnaires.
10. Dispensing of 3 cycle-related symptom questionnaires and 12 work productivity questionnaires to qualified subjects. Only subjects with protocol-defined symptoms of dysmenorrhea or PMS and who received pay for work or who volunteered were to receive work productivity questionnaires.
11. Collection of 1 cycle-related symptom questionnaire and 4 work productivity questionnaires.
    Subjects in the endometrial histology sub study underwent the following additional procedure:
12. Hemostasis panel.

Treatment Interval

Days 1 to 28
A phone call was to be made to subjects during the first pill pack (days 1 to 28) to review proper pill use (i.e. check compliance).

Days 1 to 364 (Visits 2 to 4)
Subjects and/or study personnel were to complete the following procedures during visits 2 through 4. The timing of the assessments is shown in Table 6.1-1,

1. Body weight and sitting blood pressure.
2. Urine pregnancy test.
3. ***Dispensing of home urine pregnancy test kits, diaries, and pill packs. Subjects who had a positive test result were instructed to call the site, stop taking study drug, use a back-up method of birth control, and immediately visit the site for a serum pregnancy test to confirm the positive result.***

4. Collection of diaries and pill packs. Information from the diary cards and pill packs was reviewed and recorded on the CRF.
5. Assessment of tobacco use, sexual activity, and risk for pregnancy.
6. Subject satisfaction questionnaire.
7. Assessment of adverse events.

In addition, the cycle-related symptom and work productivity questionnaires were collected from subjects in the CRSS at visits 2 and 3. These subjects continued participating as subjects in the total population after pill pack 3. The adverse event diary card dispensed at visit 1A was collected at visit 2. Subjects and/or study personnel were to complete the following additional procedures during visit 3:

1. A complete physical and gynecologic examination.
2. Laboratory safety screen (including urinalysis, hematology, and blood chemistry).
3. Cervical cytology smear.

A hemostasis panel was performed for subjects in the endometrial histology sub study at visit 3.

At visit 4, the investigator or qualified designee, as determined by the investigator, discussed and prescribed post-treatment contraception or referred the subject, as appropriate. Participation in the
1-year extension study was discussed with subjects at the Canadian sites.

Days 337 to 364 (Visit 4A)

This visit was only for subjects in the endometrial histology sub study. The following procedures were performed:

1. Body weight and sitting blood pressure.
2. Laboratory safety screen.
3. A urine pregnancy test, which must have had a negative result before the endometrial biopsy was performed.
4. Hemostasis panel.
5. Endometrial biopsy (performed after collection o of blood and urine samples). If an inadequate tissue sample was obtained from the endometrial biopsy, the investigator was to call the sponsor medical monitor for further instruction.
6. Collection of 3 diaries and pill packs.
7. Assessment of tobacco use, sexual activity, and risk for pregnancy.
8. Assessment of adverse events.

After participation in this study, eligible subjects at the Canadian sites could be chosen to participate in a 1-year extension study (0858A2-320-CA). Participants in the 1-year extension study were to continue with the LNG 90 µg/EE 20 µg continuous-use regimen for 1 year after the completion of study 0858A1-313-NA. Subjects interested in participating in the extension studies at the Canadian sites were screened during visit 4A. This visit was a transition period for subjects who were to participate in the 1-year extension study 0858A2-320-CA. Ineligible

subjects returned for the post-treatment evaluation at visit 5.

Post-treatment

Days 1 to 15 (Visit 5)

The following procedures were performed during visit 5:

1. A complete physical and gynecologic examination.
2. Mammogram for subjects 40 years or older.
3. Body weight and sitting blood pressure.
4. Laboratory safety screen (including urinalysis, hematology, and blood chemistry).
5. ***Serum β-hCG pregnancy test.***
6. Cervical cytology smear.
7. Collection of 4 diaries and pill packs (all subjects in total population and CRSS subjects only); 1 diary and pill pack were collected from subjects in the endometrial histology substudy.
8. Assessment of tobacco use, sexual activity, and risk for pregnancy.
9. Subject satisfaction questionnaire.
10. Assessment of adverse events.

If a subject reported amenorrhea after treatment, she was to continue to be evaluated at the site. Any subject not receiving hormonal therapy who had not resumed menstruation by 6 months after treatment was to be evaluated. Return to spontaneous menses was defined as at least 2 consecutive days of bleeding that required sanitary protection and that started no sooner than day 13 after the end of the treatment interval for the study.

For subjects interested in participating in the 1-year extension study 0858A2-320-CA, the visit 5 test and procedures were the screening tests and procedures conducted during pill pack 13 (days 337 to 354). This visit was a transition period for subjects entering the 1-year extension study 0858A2-320-CA. Subjects were considered to have completed study 0858A2-313-NA after they finished pill pack 13. The mammogram, laboratory safety screen, and cervical cytology smear were not performed again if they had been performed at visit 1A of this study.

Post-treatment Evaluation

All subjects who withdrew from the study with a desire to become pregnant were to be followed for 1 year or until contraception was resumed to document the return of fertility. Information on pregnancy was to be submitted on all subjects who became pregnant during the study or within 3 cycles after withdrawing from the study; this information was to include the estimated date of conception (EDC), the subject's plans for the pregnancy, and documentation on the condition of the infant. Site personnel were to document the results of any unscheduled pregnancy test in the CRF.

Subjects were eligible to participate in this study if they satisfied all of the inclusion criteria and none of the exclusion criteria.

Reviewer's Comment:
At visit 1B the subject was dispensed 2 home pregnancy test kits; some subjects also had serum pregnancy tests performed for unexpected bleeding; subjects were dispensed 3 diaries and diary cards were to be retained as source documents. All subjects received 3 pill packs at entrance into the study. This becomes critical in the review of this NDA because in a number of disputed pregnancies the documentation that the subject did not take the pills as dispensed is not clear; serum levels of hCG are not quantitated to the weeks of early gestation; in addition test article (pill) was not returned to the investigator for documentation.

Inclusion Criteria

- Healthy women aged 18-49 who were willing to rely upon the LNG90µg/EE 20µg **continuous –use regimen as their only m**ethod of contraception. No more than approximately 20% of the subjects at each site were to be older than 35 years at the time of visit A.
- Subjects were to be sexually active and at risk for becoming pregnant.
- Subjects were required to have a regular (21-35 day) menstrual cycle for the 3-month period preceding visit 1A, excluding postabortal and non-breastfeeding postpartum subjects.
- Subjects were to have had a cervical cytology smear report negative for squamous intraepithelial lesion (SIL) or malignancy at the screening visit.
- In the opinion of the investigator, the subject would comply with the protocol.
- Subjects were to provide signed and dated written informed consent.

Medical Officer's Comment:
Inclusion criteria are appropriate for this study and are consistent with the study of other OCs.

Exclusion Criteria

- Thrombophlebitis, thrombosis, or thromboembolic disorders,
- Deep vein thrombosis (DVT),
- Known coagulopathy,
- Pulmonary embolism,
- Ischemic heart disease or myocardial infarction,
- Cerebrovascular or cardiovascular disease,
- Neuro-ocular disorders (e.g. optic neuritis, or retinal vein thrombosis),
- Valvular heart disease with complications
- Cholestasis (subjects who had had a prior cholecystectomy may have been enrolled),
- Known or suspected estrogen-dependent neoplasia

- Ovarian carcinoma,
- Known or suspected carcinoma of the breast,
- Liver tumors (benign and malignant),
- Diabetes with vascular involvement or uncontrolled diabetes,
- Undiagnosed abnormal genital bleeding within the past 180 days,
- Depression requiring hospitalization or associated with suicidal ideation within the last 3 years,
- Alcoholism or drug abuse within the past 12 months,
- Hypertension with vascular involvement (e.g. hypertensive retinal changes),
- Known hypersensitivity to estrogens, progestins, or any other components of the study drug,
- **The use of Depo-Provera™ within 10 months before visit 1A or the use of Lunelle™ or** any intrauterine device or implantable contraceptive hormones within 60 days before visit 1A,
- Use of noncontraceptive estrogens, progestins, or androgens within 60 days before visit 1A,
- Use of any experimental drug or device within 60 days before visit 1A, and
- Use of any hepatic enzyme-inducing drugs, including certain anticonvulsant medications (e.g. barbiturates including Phenobarbital and primidone, phenytoin, carbamazine, oxycarbazine, felbamate, topiramate), rifampin, rifabutin, phenybutazone, **dexamethasone, St, .John's wort, modafinil, or** griseofulvin within 60 days before visit 1A and for the duration of this study.

The presence of any of the following prevented enrollment:

- Serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) level greater than 1.5 times the upper limit of normal or active liver disease,
- Hypertension, defined as sitting systolic blood pressure higher than 140 mm Hg and/or sitting diastolic blood pressure higher than 90mm Hg,
- Fasting total cholesterol level higher than 7.8mmol/L (300mg.dL) or fasting triglyceride level higher than 3.39 mmol/L (300 mg/dL),
- Planned use of any other form of birth control other than the study drug,
- Headaches with focal neurologic symptoms,
- Planned major surgery with prolonged immobilization,
- Breast mass of unknown etiology,
- Abnormality suggestive of malignancy noted on mammogram for hose subjects for whom a mammogram was required follow up for any abnormal mammogram, breast examination, or ultrasound findings,,
- Known or suspected pregnancy,
- Breastfeeding,
- Age 34 or older and smoking 15 or more cigarettes per day (US sites only); age 34 or older and smoking cigarettes (Canadian sites only), and
- Known to have positive results of testing for human immunodeficiency virus.

Subjects in the endometrial histology sub-study have the additional exclusion criteria:

- Inability to have an endometrial biopsy or insufficient endometrial tissue for histologic interpretation,
- Abnormal endometrial biopsy (e.g. hyperplasia, endometritis, or polyp), and
- Known submucosal uterine fibroids.

Medical Officer's Comment:

Exclusion criteria are generally acceptable for this study and are consistent with known contraindications for oral contraceptives. Additionally, antidepressants/ anxiolytic and antibiotic drugs which are used significantly in the general population are excluded.

Discontinuation of a subject from the study may occur for the following reasons:

- Accidental pregnancy. Site personnel were to complete the appropriate CRF for subjects withdrawing from the study because of pregnancy. The EDC, the source used to determine the EDC, and the subject's plan for the pregnancy were to be recorded on the CRF,
- Subject planning pregnancy,
- Serious adverse event, and
- If the subject missed 3 or more consecutive pill or any 5 pills during a pill pack, the investigator was to perform a pregnancy test and contact the medical monitor to discuss withdrawal of the subject from the study at that time.

All subjects who withdrew from the study with a desire to become pregnant were to be followed for one year or until contraception was resumed to document the return to fertility. Information on the pregnancy was to be submitted on all subjects who became pregnant during the study or within 3 cycles after withdrawing from the study; this information was to include the EDC, the subject's plans for the pregnancy and documentation on the condition of the infant.

The study drug was dispensed as a 28-day pill pack, each pill contained LNG 90µg/EE 20µg. Each subject was to begin taking study drug on the first day of her menstrual cycle (first pill pack only) and was to continue taking 1 pill daily, orally, for approximately 1 year at approximately the same time each day; there were no pill-free intervals.

Prohibited Therapy

The use of the following medications was prohibited during the study:

- Sex hormones (except those give in this study),
- Forms of birth control other than the study drug (permission for medically indicated condom use could have been granted by the investigator),
- Any hepatic enzyme-inducing drugs, including certain anticonvulsant medications (e.g. barbiturates including phenobarbital and primidone, phenytoin, carbamazepine, oxcarbazepine, felbamate, topiramate), rifampin, rifabutin, phenybutazone,

dexamethasone, St. John's wort, modafinil, or griseofulvin within 60 days before visit 1A and for he duration of the study.

- Use for more than 14 days of anti-infectives that alter the intestinal flora (e.g. ampicillin and tetracycline), and
- Drugs requiring the simultaneous use of contraceptives in their labeling (e.g. isotretinoin **[Accutane™]).**

Additional prohibited treatment for subjects in the endometrial histology sub study:

- Prescription anticoagulants within 30 days before visit 1A and for the duration of the study, and
- Chronic use of aspirin or any aspirin-containing medication for the 2-week period before all blood sample collections.

Medical Officer's Comment:
The discontinuation list of subjects for this study is consistent with other oral contraceptive. The prohibited therapies are the usual medications that are included in the class label for oral contraceptives and these medications have been reported to decrease the effectiveness of oral contraceptives.

Treatment Compliance

During the study subjects were given diary card on which to record the day that the study drug was taken or missed. If a subject missed 3 or more consecutive pills, or any 5 pills during one pill pack, the investigator was to perform a pregnancy test and contact the medical monitor to discuss withdrawal of the subject from the study.

Discontinuation Rates

Subjects who withdrew from the study ***were not to be replaced***, regardless of the reason for withdrawal. An effort was made to determine why a subject failed to return for the necessary visits or withdrew from the study. This information, in addition to the date of discontinuation, **was recorded on the subject's CRF.**

Pregnancy Rates

Pregnancy rates were computed by means of the Pearl index and Life table methods to determine the contraceptive effectiveness of the LNG µg/EE µg continuous use regimen. Analyses of the contraceptive efficacy were performed for all subjects and then separately for subjects who were 35 years of age or younger at the beginning of the study.

Life table analyses of pregnancy rates were performed to determine the cumulative risk of pregnancy over time. The pregnancy rate was computed for each pill pack as well as cumulatively from the first pill pack to each subsequent pill pack, by calculation of the conditional probabilities of becoming pregnant or continuing use.

Pill packs that were excluded from the Pearl's index and any subsequent pill packs were excluded from the life table analyses. Life tables were produced for method failure, user failure, and overall pregnancy rates.

Determination of Sample Size

Approximately 2000 subjects were to be enrolled in this study. Of these subjects, approximately 308 were also to participate in the 3-month CRSS and approximately 125 were to participate in the endometrial histology sub-study. The total planned number of enrolled subjects was consistent with regulatory requirements for contraceptive and was based on an estimated annual dropout rate of 50%.

Reviewer's Comment
It appears that the pre-study prediction of the anticipated drop out rate is very high. (Usually the drop out rate for combined oral contraceptives is predicted to be on the order of 20%-35%); however, this drop out rate may have been based on what was demonstrated with Seasonale (50%).

Of the 125 subjects planned for enrollment in the endometrial histology sub-study, approximately 65 were expected to have biopsies done at baseline and after treatment pill pack 13. The number of subjects was based on clinical considerations and not on statistical power.

Changes in the Conduct of the Study or Planned Analyses

Per the Sponsor their protocol-specified Pearl index calculation as previously outlined was based **upon Wyeth's understanding of the most recent** U.S. approval for an oral contraceptive. However, ***according to the sponsor*** when data on return to ovulation is taken into consideration (protocol 208) it became apparent that the inclusion of this time period yields potentially misleading results. Therefore, 2 additional Pearl index calculations were provided to better assess the contraceptive efficacy of this continuous-use regimen. One calculation excluded all pregnancies that occurred after study drug had been discontinued (preferred by sponsor) and the other included pregnancies that occurred within 7 days after the last day of study drug.

Reviewer's Comment
This reviewer is not in agreement with the sponsor's assertion that the Pearl index (including days 1 to 14) used by the Division over the last 6-7 years is not appropriate and might lead to misleading results. Other sponsors at the NDA stage and the pre-NDA guidance had adopted the Divisions recommendation. Other lower dose products have adopted the Division's 14 day cutoff and these products were successful in their approvals.

Study Procedures

Study procedures for subjects from pre-study to post-treatment are outlined in the following table from the sponsor:

Table 3 Study Flow Chart

Table 6.1-1: Study Flowchart

	Pretreatment		Treatment Interval							Posttreatment
Visit	1A[a]	1B[a,b]		2		3		4		5[c]
Days	5-18	12-26	1-56	57-84	85-168	169-196	197-252	253-280	281-364	1-15
Pill Packs			1, 2	3	4, 5, 6	7	8, 9	10	11, 12, 13[d]	
Informed consent/history	X									
Inclusion/exclusion criteria	X	X								
Physical and gynecologic examination	X					X				X
Mammogram (if needed)[e]	X									X
Body weight/sitting blood pressure	X	X		X		X		X		X
Laboratory safety screen	X					X				X[f]
Chlamydia screening test[g]	X									
Serum β-hCG[h]	X									X
Urine pregnancy test[h]		X	X	X	X	X	X	X	X	
Cervical cytology smear	X					X				X[i]
Dispense home urine pregnancy test kit[j]		2		3		2		3		
Dispense adverse event diary[k]	1									
Dispense diaries		3		4		3		3[l]		
Dispense pill packs		3		4		3		3		
Collect adverse event diary[m]				1						
Collect diaries				2		4		3		4
Collect pill packs				2		4		3		4
Assess tobacco use and sexual activity	X	X		X		X		X[n]		X
Subject satisfaction questionnaire	X			X		X		X		X
Assess adverse events	X-									-X
Phone call			X[o]							

Note: Subjects in the study were to take 1 pill daily for 1 year. Subjects who did not qualify for the cycle-related symptom substudy could continue to participate as a subject in the total population if they met all other criteria.

a. Visit 1A and 1B were to occur within the same cycle.
b. Results from visit 1A testing must have been available by visit 1B.
c. Visit 5 was to occur between days 1 and 15 after day 364 or the last dose of study drug. Any remaining pill packs and diaries were to be returned to the site at this visit.
d. For subjects interested in participating in the 1-year extension study (0858A2-320-CA), the tests and procedures performed during pill pack 13 (days 337 to 354; visit 4A) served as the screening tests and procedures at visit 5. This visit was to be a transition period into the 1-year extension study 0858A2-320-CA.
e. A mammogram was required for subjects who were aged 40 years or older at visit 1A or who would turn 40 during the course of the study. A mammogram within 6 months before visit 1A was acceptable for these subjects if a copy of the report was obtained and results were recorded on the case report form. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the mammogram did not need to be repeated at visit 5 if it had been performed at visit 1A in this study.
f. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the laboratory safety screen did not need to be repeated at visit 5 if it had been done at visit 1A in this study.
g. A chlamydia test was required for subjects aged 25 years or younger and other subjects who had risk factors for chlamydia, as determined by the investigator at visit 1A. If results were positive, the investigator was to provide the subject with the appropriate treatment. A positive test result did not preclude the subject from participating in the study.
h. A serum β-hCG pregnancy test was required at visit 1A and the final visit. A urine pregnancy test was to be performed at all other visits and as indicated to exclude pregnancy.
i. For subjects who were ineligible for the 1-year extension study 0858A2-320-CA, the cervical cytology smear did not need to be repeated at visit 5 if it had been done at visit 1A.
j. Subjects were instructed to use the home urine pregnancy test kit to check for pregnancy during pill packs in which there were no scheduled visits.
k. One (1) diary card was to be dispensed at visit 1A for the assessment of adverse events (symptoms and complaints).
l. For subjects who were transitioning into the 1-year extension study 0858A2-320-CA, diaries for pill packs 11 and 12 and if applicable for pill pack 13 were dispensed. For those subjects given a diary for pill pack 13, the white ply was to be returned to the study site in a prepaid envelope.
m. The adverse event diary card dispensed at visit 1A was to be collected at visit 2.
n. Posttreatment contraception was to be discussed with all subjects. Participation in the 1-year extension study 0858A2-320-CA was to be discussed with subjects at the Canadian sites.
o. A phone call was to be made during the first pill pack (days 1 to 28) to review proper pill use (ie, check compliance).

Disposition of Subjects:

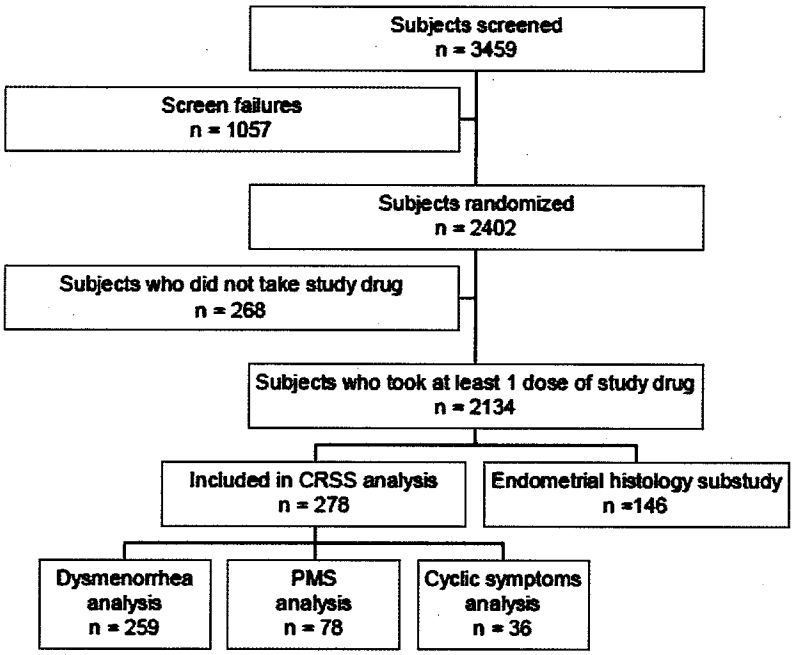
Written informed consent was provided by 459 subjects who were screened for evaluation of eligibility. Screening failures were 1,057. A total of 2,402 subjects were randomly assigned to study drug. Of this total, 2,134 subjects took at least 1 dose of study drug (total population), including 1,762 subjects who were age 35 years or younger at study start. A total of 146 subjects participated in the endometrial histology sub-study. The disposition of subjects is shown in the

following figure (Note no subjects are included in this review that were enrolled in the CRSS analysis, the dysmenorrhea analysis, the PMS analysis or the cyclic symptoms analyses. The Figure 1 is sponsor's figure 8.1-1

b(4)

Figure 1 Disposition of Subjects

Figure 8.1-1: Disposition of Subjects



Discontinuations

A total of 1,213 (56.8%) subjects discontinued study drug and withdrew from the study. The primary reasons for these discontinuations are summarized in the table below:

Appears This Way
On Original

Table 4 The primary reasons for discontinuations Sponsor's table 8.1.1-1

Reason	LNG 90 µg/EE 20 µg Continuous-Use Regimen
Total	2134 (100)
Completed	921 (43.2)
Discontinued[a]	1213 (56.8)
Accidental pregnancy	19 (0.9)
Adverse event[b]	363 (17.0)
Discontinuation of study by sponsor	102 (4.8)
Investigator request	11 (0.5)
Lost to follow-up	223 (10.4)
Planning pregnancy	19 (0.9)
Protocol violation	140 (6.6)
Subject request	336 (15.7)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.
a: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
b: Total includes subject 313-091-8311, who did not have a specific event identified on the case report form. Adverse event was listed on the termination record for this subject but no event was specified and no adverse event was identified on the adverse event case report form as the reason for withdrawal.
CDR CPP4; 28JAN05 15:02

Note 2,134 subjects 921 (43.2%) completed this study; there were 1,213 (56.8%) subjects who discontinued from this study due to any AE. To **this reviewer's knowledge, this is the lowest** total number of subjects completing a 13-cycle study and is the highest total discontinuation of an OC in a 13-cycle OC trial that has been reviewed in this Division. Also, note that 363 (17%) of subjects discontinued due to an AE. Of the 363 subjects who discontinued due to bleeding episodes, 181 (49.8%) discontinued due to bleeding related AEs. Significantly, another 336 (15.7%) of subjects discontinued due to subject request (which in review of many CRF were subjects who were having bleeding problems but not to an extent that it was listed and an AE).An additional 223 (10.4%) were lost to follow-up; although this is not an inconsistent number from other OC products it usually reflects some problem with the medication or a major move somewhere else. An additional 102 (4.8%) **subject's discontinued because the study** treatment was ended by the sponsor.

The demographic and baseline characteristics were summarized in Table 8.2.1-1 (not reproduced). This table reports the total study population of 2,134 subjects. Of this total 1,646 (77.13%) were white, 217 (10.17%) were black, 188 (8.81%) were Hispanic, 33 (1.55%) were Asian, and 50 (2.34%) were described as other. The mean age was 28.77 years. The mean height was 164.39 ± 666 cm. the mean weight was 70.38±16.83 kg and the body mass index was 26.04±6.07. Additionally, 911 (42.69%) of subjects had no pregnancies, 465 (21.79) were nulliparous, 399 (18.70%) had been pregnant twice, 205 (9.61%) had been pregnant three times, 91 (4.26%) had been pregnant 4 times, 40 (1.87%) had been pregnant 5 times, and an additional 23 subjects had been pregnant from 6-11 times. There were 1,694 (79.38%) subjects who were non-smokers and 440 (20.62%) who were smokers. In the smoking group subject smoked on average 7.54 cigarettes per day. Subjects on average had 14.59 ± 2.27 years of education. Subjects were reported to have been on study drug 237.26 ± 129.25 days and 1,023 (58.06) subjects did not complete the study while 921 (43.16%) completed the study.

Of the 2,134 subjects in the total population, 1,762 were aged 35 years or younger at the time of enrollment. These subjects had demographic and baseline characteristics (i.e. race, height,

weight, BMI, and previous pregnancies) similar to those to the total population, but were younger with a mean age of 26.43 years; there were more nulliparous subjects in the <35 age group were 47.33% vs. 42.69%, otherwise the groups were very similar.

Reviewer's Comment
Subjects who desired contraception in this study are consistent with other studies. Importantly, the sponsor did not give a breakdown of new acceptors compared to switchers from OC use. New acceptors are more likely to experience AEs since they have not been exposed to the new combination and switchers are likely to have less severe AEs because they have already been exposed to similar estrogen/progestin combinations. Therefore, compared to a new progestin/estrogen combination less serious AEs can be anticipated, especially if the estrogen dosage is at 20μg or 25μg of EE.

Concomitant Therapy

A total of 1,897 (88.9%) of subjects used concomitant non study medications. The most frequently used class of concomitant therapy were antiinflammatory/antirheumatic products, nonsteroidals (1,222 subjects, 57.3%), analgesics and antipyretics (1,077 subjects, 50.5%), antihistamines for systemic use (544 subjects, 25.5%), and combinations multivitamins (345 subjects, 16.2%), antidepressants (265 (12.4%), nasal decongestants for systemic use 256 (12.0%), beta-lactam antibacterials, penicillins 212 (9.9%), macrolides and lincosamides (197 (9.2%) and opioids 171 (8.0%). Other classifications, such as antitussives, drugs to treat peptic ulcer, nasal decongestants for topical use, etc. had between 7 and 5% usage.

Reviewer's Comment:
Use of concomitant medications is consistent with that seen in other OC studies.

Efficacy Evaluation

A total of 18,710 pill packs were reported for the 2,134 subjects in the total study population. Of pill packs reported a total of 15, 461 (83%) were included in the Pearl index analyses and 11,295 (60%) were included in the Life table analyses of contraceptive efficacy.
The following tables report the breakdown of the number of excluded pill packs from the Pearl index analyses and Life table analyses:

Table 5 Number (%) of Pill Packs Excluded from Pearl Index Analyses of Contraceptive Efficacy by Reason: Total Population Sponsor's Table 9.1.1-2

Reason	Number (%) Pill Packs
Pill packs included	15, 461 (83)
Pill packs excluded[a]	3249 (17)
Backup contraception used (or unknown)	1640 (9)
Missed ≥ 3 consecutive pills	111 (< 1)
Missed ≥ 5 pills total in any 1 pill pack	128 (< 1)
Prohibited medication	323 (2)
Not sexually active (or unknown)	1212 (6)
Pregnant before pill pack start	17 (< 1)

a: A pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason for exclusic applied was excluded.

Table 6 Number (%) of Pill Packs Excluded from Life Table Analyses of Contraceptive Efficacy by Reason: Subjects in the Total Population Sponsor's Table 9.1.1-3

Reason	Number (%) Pill Packs
Pill packs included	11,295 (60)
Pill packs excluded[a]	7415 (40)
Backup contraception used (or unknown)	4465 (24)
Missed ≥ 3 consecutive pills	286 (2)
Missed ≥ 5 pills total in any pill pack	322 (2)
Prohibited medication	467 (2)
Not sexually active (or unknown)	2233 (12)
Pregnant before pill pack start	17 (< 1)

a: A pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason applied a any subsequent pill packs were excluded.

Note the difference between the two tables. In the Pearl index analyses there were 15,461 (83%) pill pack included and 3,249 (17%) of cycles were excluded from the analyses with the largest group being subjects who used backup contraception 1,640 (9%) and subjects who were not sexually active 1,212 (6%). In the Life table analyses there were 11,295 (60%) pill packs included and 7,415 (40%) of pill packs were excluded with the largest percentage being subjects who used backup contraception 4,465 (24%) and subjects who were not sexually active 2,233 (12%). Roughly twice as many subjects were excluded in the Life table analyses (because they were not sexually active, used backup contraception, and once the censored event occurred had the remaining cycles excluded) compared to the Pearl index analyses. It would be expected that with lesser total pill packs included in the Life table analyses the pregnancy rate would be higher than the Pearl index since the number of evaluable pill packs is decreased by 4,166 pill packs.

The following two tables show the number (%) of pill packs excluded from the Pearl index analyses of contraceptive efficacy by reason for the age group 35 or younger; ***this is the population considered for effectiveness:***

Table 7 Number (%) of pill Packs Excluded from Pearl Index Analyses of Contraceptive Efficacy by Reason: Subjects Aged 35 years or Younger---Sponsor's Table 9.1.2-2

Reason	Number (%)
Pill packs included	12,572 (82)
Pill packs excluded[a]	2681 (18)
Backup contraception used (or unknown)	1393 (9)
Missed ≥ 3 consecutive pills	87 (< 1)
Missed ≥ 5 pills total in any 1 pill pack	106 (< 1)
Prohibited medication	222 (1)
Not sexually active (or unknown)	1008 (7)
Pregnant before pill pack start	16 (< 1)

a: A pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason for exclusion applied was excluded.

Table 8 Number (%) of pill Packs Excluded from Life Table Analyses of Contraceptive Efficacy by Reason: Subjects Aged 35 Years or Younger Sponsor's 9.1.2-

Reason	Number (%)
Pill packs included	9180 (60)
Pill packs excluded[a]	6073 (40)
Backup contraception used (or unknown)	3735 (24)
Missed ≥ 3 consecutive pills	229 (2)
Missed ≥ 5 pills total in any 1 pill pack	283 (2)
Prohibited medication	308 (2)
Not sexually active (or unknown)	1816 (12)
Pregnant before pill pack start	16 (< 1)

a: A pill pack may have been excluded for more than 1 reason; the pill pack to which the reasons applied and a subsequent pill packs were excluded.

Again note the difference between the two tables. In the Pearl index analyses the total number of cycles included was 12,572 (82%); 2,681 (18%) of cycles were excluded from the analyses with the largest group being subjects who used backup contraceptive 1,393 (9%) and an additional 1,008 subjects who were not sexually active. In the Life table analyses the total number of pill packs included was 9,180; 3,735 (24%) subjects were excluded from the analyses because they used backup contraception, an additional 1,816 (12%) were not sexually active, and once the censored event occurred the remaining cycles were excluded. Note 40% of pill packs were excluded in the Life table analyses compared to 18% in the Pearl index analyses. It would be expected that with lesser total pill packs included the Life table analyses compared to the Pearl index the pregnancy rate would be higher since the number of evaluable pill packs is decreased by 3,392 pill packs.

Treatment Compliance

At least one pill was missed in 3,559 (19%) of the 18,710 pill packs. The vast majority of missed pills were in pill packs for which either one pill was missed (12%) or two pills were missed (5%). Pill packs with five or more missed pills (protocol violation) occurred with 0.5% of the pill packs. If compliance is reviewed in another manner, on average approximately 1.18 days of pills were missed over the study; there appeared to be ***little difference*** between pill pack cycle 1 (1.22) versus pill pack 12 (1.10).

The following table reports the pregnancy rates that occurred on-therapy, including those pregnancies not classified as a method ***or*** user failure.

Table 9 Summary of Sponsor's Pregnancy Classification Included in the Analyses of Contraceptive Efficacy
Sponsor's Table 9.4.2.1-1

Subject	Pregnancy Classification[a]	Total Duration of Study Drug	Estimated Date of Conception (Relative Day)
LNG 90 µg/EE 20 µg Continuous-Use Regimen			
313-019-1102	Method failure	340	
313-025-1735	Method failure	168	
313-030-2210	Method failure	74	
313-034-2604	Method failure	139	
313-044-3610	Method failure	364	
313-047-3931	Method failure	259	
313-051-4313	Method failure	148	
313-052-4416	Method failure	133	
313-057-4924	Method failure	136	
313-064-5612	Method failure	196	
313-064-5627	Method failure	79	
313-064-5643	Method failure	247	
313-084-7604	Method failure	308	
313-091-8312	Method failure	364	
313-098-9714	Method failure	84	
313-070-6224	Not classified[b]	56	Posttreatment
313-079-7109	Not classified[b]	334	Posttreatment
313-074-6614	Not classified[b]	186	Posttreatment
313-024-1603	User failure	185	
313-029-2127	User failure	72	
313-074-6611	User failure	51	
313-086-7817	User failure	334	
313-072-6440	Not classified[c]	84	Posttreatment

b(4)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.

a: An on-treatment pregnancy was attributed to "method failure" if the subject took 100% of her assigned dose within the 30 days before the EDC and did not take prohibited medication. The pregnancy was attributed to "user failure" if the subject was compliant with the protocol with respect to taking study drug and did not take prohibited medication (see section 6.4.7.2); the subject could have missed up to 2 consecutive days of pills or up to 4 total days within the 30 days before the EDC.

b: Not classified for Pearl Index. Subject was 100% compliant with respect to taking study drug within 30 days before EDC (including the posttreatment portion of that 30-day period, when study drug was not taken), and was classified as a method failure for the life table analysis.

c: Not classified for Pearl Index. Subject was compliant with the protocol but she reported that she had missed several pills in the month before conception and was classified as a user failure for the life table analysis.

There were 23 pregnancies reported by the sponsor under the categories method failure, not classified, user failure and not classified. Under these categories the sponsor reported 15 method failures, 3 not classified, 4 user failures, and one as not classified (as to Pearl index).Also note 3 of the 4 pregnancies who were unclassified with respect to Pearl index occurred in women who had been 100% compliant with the test drug and conceived 1, 8, and 12 days, respectively after discontinuing the drug. Note that pregnancies occurred throughout the clinical trial from the 2nd cycle (subjects 313-070-6224, 313-074-6611) to almost one year of the study (subjects 313-019-1102, 313-091-8312, 313-079-7109, 313-086-7817). This is unusual in OC trials because most

pregnancies normally occur ***within the first 6 cycles*** in the treatment period because the subjects tend to be less familiar with the treatment therapy and are more apt to miss pills. As the subject improves pill taking and pregnancies become less frequent ***if there is inherent good suppression by the OC***. It there is less suppression of ovulation the subject is penalized with a pregnancy because the lower dose of the progestin tends ***not to fully suppress*** ovulation. Pregnancies throughout the treatment period suggest that at each cycle the subject may become pregnant if she misses ***any*** of her pills. This appears to be the **case with Lybrel™, where suppression does** not appear to be as effective as with the subject receiving 150mcg of levonorgestrel (e.g. Seasonale). As stated earlier, all pregnancies that occurred ***within 14 days of termination from the study*** will be reviewed as having occurred within the study (this is consistent with other more recently approved oral contraceptives).

After review of pregnancies reported by the sponsor that includes pre-therapy, on-treatment, and post-therapy this reviewer is evaluating 7 additional pregnancies as likely to have occurred during the on-therapy time period. In the pre-therapy group subjects 313-067-005924 and 313-091-8347 are added to the sponsor total. In the pre-therapy group, subject 313-067-5924 and subject 313-091-8347 did not return test article even through there appears to have been telephone contact between the sponsor and the subjects. Subject 313-067-59-24 was also placed in the lost- to follow- up group. In the post-therapy group, subjects 313-034-002607 and 313-001-8578, 313-011-0323, 313-052-4421 and subject 313-074-6604 are added because this reviewer was unable to confirm that these subjects were not receiving test drug and the ultrasound and hCG testing were unable to assure these subjects were not pregnant while taking test drug or had stopped the pill within 14 days of getting pregnant.

The following is a short synopsis of pregnancies that occurred in the post-therapy period:

Subject 313-034-2607 started test meds on May 23 2003 and concluded her meds on May 21, 2004. Her diary data confirms she kept a good diary and rarely missed an OC in her year in the study. An ultrasound performed on [redacted] confirmed a pregnancy of 8 weeks 0 days. Counting backward it places the expected date of conception at [redacted] This is within [redacted] after the subject finished her OCs, therefore, it falls within the 14 days period for counting an in-treatment pregnancy. b(6)

Subject 313-001-8578 started test meds on September 7, 2003 and may have finished on November 18, 2003. The subject should have finished her pill pack on November 29, 2004, but she missed several pills throughout this cycle. An ultrasound dated the pregnancy date at [redacted]. This places this subject within the <14 days that account for an in-treatment pregnancy. b(6)

Subject 313-011-0323 started in the study on August 9, 2003 and was discontinued from the study on December 16, 2003. Subject missed pills on 3 days in November 2003, but pills were taken until November 30, 2003. On [redacted] she reported a positive pregnancy test. The estimated date of conception was [redacted]. Study medication were being taken within the <14 day period even though she was b(6)

discontinued by the investigator. The ultrasound performed on [redacted] was not confirmatory of any pregnancy; no retained products of conception were found.

Subject 313-0520-4421 started her meds on June 29, 2003 and finished in the study on June 26, 2004. On [redacted] the subject had a positive pregnancy test. The earliest ultrasound was on [redacted] which placed her at [redacted]. Using the ultrasound and staying within the <14 days period the date of conception [redacted] would [redacted]. This is within 14 days of stopping the medication. b(6)

Subject 313-074-6604 started in the study on June 1, 2003 and finished the study on March 6, 2004. It is stated that the subject stopped taking study meds on May 31, 2004 but she provided no diary pages to show study meds from March 7 to May 31, 2004. On [redacted] the subject had a negative urine pregnancy test and a positive serum pregnancy test on [redacted] that is written in CRF. An ultrasound on [redacted] recorded an intrauterine pregnancy of [redacted]. The ultrasound would place the conception date on [redacted] as recorded by the sponsor. There is clearly a discrepancy between what the sponsor recorded and the ultrasound and it may relate to the fact of uncertainty as to when the subject actually stopped her pills. Therefore, unless the subject medical record is available for review, this case will be considered an in-treatment pregnancy. b(6)

The following is a brief summarization of subjects with discrepant data that is not confirmed and is disputed with the sponsor:

Table 10 Synopsis of Disputed Pregnancies

Study Subject	Start OCP	Stop OCP	On treatment time period (≤14 days)	Calculated Conception
313-034-2607	6/23/03	5/20/04	6/3/04	
313-001-8578	9/7/03	11/29/03	12/13/03	[redacted]
313-011-0323	8/9/03	11/26/03	12/14/03	
313-052-4421	6/29/03	6/26/04	7/10/04	
313-074-6604*	6/1/03	3/06/04??	Uncertain-	
313-039-3159**	8/24/03	2/26/04	3/12/04	
313-029-2118**	No pregnancy confirmed via investigator letter			
313-067-5924+	Test article not returned			
313-091-8347++	Test article not returned			

b(6)

*Subject presented no diary pages after May 31, 2004 but continued in the study until August 19, 2004. Exact data of pregnancy is unsure, especially since there is only a second trimester ultrasound.

**Documentation supplied of conception via requested ultrasound or investigator letter
+ Subject was in study for 99 days without recovery of test article. Statement made as pregnancy dating yet claim is made subject loss to follow-up
Test article given; date and results of serum pregnancy test were not done.

The final review determined Pearl index and Life table analysis for study 313NA is based on 30 pregnancies that were defined by the sponsor and modified by FDA as occurring pre-therapy, on-therapy, and post-therapy pregnancies. These analyses have been done with full consultation from the statistical team.

Table 11 On-Therapy Pearl index and Age ≤ 35 years old--Study 313-NA

On-Therapy Pearl Index : Total Population and Aged ≤35 years old in Study 313-NA.				
Failure Type	Analysis Population	Number of		Pearl Index
		Pregnancies	Pill packs	
On-Therapy (≤14 days post	All Ages:			
	ITT (Sponsor's)	23	15,461	1.93
	Modified ITT (FDA)*	30	15,463	2.52(CI1.70,3.59)
	Aged ≤35:			
	ITT (Sponsor's)	23	12,572	2.38
	Modified ITT (FDA)	30	12,574	3.10(CI2.09,4.41)
*** FDA's Analysis included 7 additional pregnancies (2 pre-therapy, 5 post-therapy)**				

Amenorrhea and Bleeding Episodes

The initial reason given by the sponsor for the development of the continuous use oral contraceptive was that without a 7-day withdrawal period a subject could have sustained anovulation and therefore sustained amenorrhea so that bleeding could or would not enter into her daily activities. Further, the sponsor reasoned that by eliminating menses on a monthly basis the symptoms relating to withdrawn of hormones or natural menses such as cycle related symptoms, could be lessen in an effort to improve a woman's quality of life. This is the reason why the sponsor also studied CRSS (cycle related symptom sub study) and dysmenorrhea in this study. [redacted] This following section b(4) reports on the success of the sponsor in achieving amenorrhea. The following table shows the incidence if amenorrhea and no bleeding (with or without Spotting)

Table 12 Incidence of Amenorrhea and No Bleeding (With or Without (Spotting) Per Pill Pack Number and Percentage of Subjects per Pill Pack with 28 Days of Data Sponsor's Table 9.4.2.2.1-1

Pill Pack	n	Amenorrhea [a] n (%)	No Bleeding (With or Without Spotting) n (%)
LNG 90 µg/EE 20 µg Continuous-Use Regimen			
1	2048	48 (2.3)	124 (6.1)
2	1947	450 (23.1)	936 (48.1)
3	1671	446 (26.7)	878 (52.5)
4	1545	502 (32.5)	927 (60.0)
5	1469	540 (36.8)	943 (64.2)
6	1403	555 (39.6)	929 (66.2)
7	1220	546 (44.8)	864 (70.8)
8	1173	600 (51.2)	891 (76.0)
9	1144	601 (52.5)	870 (76.0)
10	1070	584 (54.6)	841 (78.6)
11	1014	597 (58.9)	821 (81.0)
12	977	604 (61.8)	816 (83.5)
13	860	505 (58.7)	679 (79.0)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.
a: Amenorrhea = no bleeding or spotting.

Note at cycle 6, 555 (39.6%) of subjects become amenorrheic. Looking at this another way, between 5-6 months of treatment, 60.4% of the 1,403 subjects are not amenorrheic at cycle 6 and are experiencing some spotting. Additionally, at 6 months the number of subjects in the trial has decreased from 2,134 to 1,403 (44.3%). At cycle 13, 505 (58.7%) of subjects become amenorrheic while 355 (41.3%) are still experiencing spotting. Although by cycle 13 an improvement is shown, greater than 58% of subjects are no longer in the study and a significant number are still spotting at cycle 13 and ***are not amenorrheic***.

Table 13 Cumulative Rates of Amenorrhea at Each Pill Pack: Subjects with Complete Bleeding Data through Pill Pack 13.....Sponsor's table 9.4.2.2.2-1

Pill Packs	Number (%) (n=779)	(95% CI)
LNG 90 µg/EE 20 µg Continuous-Use Regimen		
1 to 13	5 (0.6)	(0.2, 1.5)
2 to 13	54 (6.9)	(5.3, 8.9)
3 to 13	75 (9.6)	(7.6, 11.9)
4 to 13	93 (11.9)	(9.7, 14.4)
5 to 13	114 (14.6)	(12.2, 17.3)
6 to 13	131 (16.8)	(14.3, 19.6)
7 to 13	163 (20.9)	(18.1, 24.0)
8 to 13	204 (26.2)	(23.1, 29.4)
9 to 13	238 (30.6)	(27.3, 33.9)
10 to 13	274 (35.2)	(31.8, 38.6)
11 to 13	335 (43.0)	(39.5, 46.6)
12 to 13	387 (49.7)	(46.1, 53.2)
13 to 13	454 (58.3)	(54.7, 61.8)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol; CI = confidence intervals.

Note that by end of cycle 3, 75 (9.6%) of subjects achieve amenorrhea; by the end of cycle 6, 131 (16.8%) of subjects achieve amenorrhea and by the end of cycle 13, 454 (58.3%) of the remaining subjects are amenorrheic. Similar to the previous table this reviewer notes that 41.7% of subjects have not achieved amenorrhea and are still bleeding or spotting.

Table 14 Incidence of Bleeding and Spotting per Pill Pack: Number and Percentage of Subjects per Pill Pack with 28 days of Data Sponsor's Table 9.4.2.3.1-1

Pill Pack	n	Bleeding (With No Spotting) n (%)	Spotting (With No Bleeding) n (%)	Bleeding and/or Spotting n (%)	Bleeding (With/Without Spotting) n (%)
LNG 90 µg/EE 20 µg Continuous-Use Regimen					
1	2048	254 (12.4)	76 (3.7)	2000 (97.7)	1924 (93.9)
2	1947	114 (5.9)	486 (25.0)	1497 (76.9)	1011 (51.9)
3	1671	105 (6.3)	432 (25.9)	1225 (73.3)	793 (47.5)
4	1545	88 (5.7)	425 (27.5)	1043 (67.5)	618 (40.0)
5	1469	65 (4.4)	403 (27.4)	929 (63.2)	526 (35.8)
6	1403	74 (5.3)	374 (26.7)	848 (60.4)	474 (33.8)
7	1220	43 (3.5)	318 (26.1)	674 (55.2)	356 (29.2)
8	1173	32 (2.7)	291 (24.8)	573 (48.8)	282 (24.0)
9	1144	31 (2.7)	269 (23.5)	543 (47.5)	274 (24.0)
10	1070	34 (3.2)	257 (24.0)	486 (45.4)	229 (21.4)
11	1014	17 (1.7)	224 (22.1)	417 (41.1)	193 (19.0)
12	977	20 (2.0)	212 (21.7)	373 (38.2)	161 (16.5)
13	860	23 (2.7)	174 (20.2)	355 (41.3)	181 (21.0)

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.

Note the number of pill packs at cycles 6, 9 and 13. In all of these cycles subjects are reporting bleeding, bleeding without spotting, bleeding with spotting and these totals are opposite to those reported for amenorrhea. The third column clearly demonstrates the subjects who are bleeding and spotting as a total percent of the original 2,048. Although the percent of bleeding/spotting at cycle 12 and 13 is recorded as 38.2% to 41.3%; note that the subjects have declined to 977 at

cycle 12 and 860 at cycle 13. These subjects are clearly the survivors of 13 cycles of spotting and bleeding and only 41.9% still remain in the study.

6.1.5 Clinical Microbiology

There were no clinical microbiology issues identified in this study.

Identity of Investigational Product

Table 15 Product Information

Investigational Product	Formulation	Batch Number	Site of Manufacture
LNG 90 µg/EE 20 µg tablets	0931760C	A22646	Guayama, Puerto Rico
	0931921C	A59604	Guayama, Puerto Rico
LNG 100 µg/EE 20 µg tablets	0931845C	A16503	Newbridge, Ireland
	0931845C	A16504	Newbridge, Ireland
	0931845C	A47337	Newbridge, Ireland

6.1.6 Efficacy Conclusions

To support my conclusion regarding efficacy I will present a discussion of the cross-study comparisons of the discontinuation rates for similar lower dose OCs and cross-study comparisons of the Pearl indices for similar lower dose products. Finally I will put the specific **Pearl index and Life table analyses for Lybrel™** in perspective to these comparisons with other products. The following table shows similar 20-30 mcg OCs that are presently on the market, have recently been approved, or are in the pipeline for approval:

Table 16 Study discontinuation rates (%) for 20-30 mcg dose OCs

LN90 EE20	Alesse * LN 100/ 20EE	Lo-Estrin NET 100 20EE	Mircette DES0 150/EE20 10EE (days 24-28)	Cyclessa DESO 100/125/150 EE25	Ortho TriCyclenLo NORGES 180/215/250 EE25	Nordette LN150 EE30	Seasonale LN150 EE30	YAZ 20DESO 20EE	Lo-Estrin/24* NETA100/ EE20
56.8	9.0	25.6	47.0	18.2	25.6	28.8	40.6	5.6	22

* 6-month cycle trial
Some of these discontinuation rates have been complied in more recent comparative trials used to supplement approval of lower dose 0Cc (%)

The previous highest discontinuation rate presented in a clinical trial was that of Mircette® at 47.0%. Other products range between a low of 5.6% (Yaz®) to 25.6% for Loestrin® and Ortho TriCyclenLo®. All of these products contain 20-25mcg of EE. Note that the discontinuation rate **of Lybrel™ is 56.8%. Quoting Contraceptive** Technology and guided by several similar published articles it is clear that ***"Many pregnancies occur when women discontinue OCs, fail to begin another method of contraception and, therefore, have unprotected intercourse."*** Many

studies support the concept that increased discontinuation rates lead to unwanted pregnancies and have a serious health impact upon this country[2]. In this study subjects were clearly discontinuing this method of contraception because of unexpected, unanticipated and unpredictable bleeding. This is sustained by the fact that there is poor cycle control with this method. It is not until month 8 when >50% those subjects still in the study achieve amenorrhea [(N=1,173, n= 600 (51.2%)]. (See Table10). Note that at month 8 there is slightly greater than half the subjects (54.9%) in the study from the original 2,134.

Referring to Table 11, in study 313-NA (the reviewer**'s modified intent to** treat [ITT]) analysis of the Pearl index in the 18-35 age group is ***3.10*** (CI 2.09, 4.41). The Pearl index for the all age groups is ***2.52*** (CI 1.70 3.59). The corresponding Life table analyses in the 18-35 age group is ***0.0423*** (CI 0.0284, 0.0626) and 0.0342 (CI 0.0230, 0.0506) in the total population, respectively. In this case the Life table analysis appears to be more accurate and consistent with the total number of pill use cycles and treatment as would be seen ***in real world use***. A discrepancy of > 1 between the Life table and the Pearl index is significant and this reviewer is unaware of any other such discrepancy for oral contraceptives
The following table shows the Pearl index of a number of comparable lower dose OCs

Table 17 Pearl Indices for Comparative Low-Dose OCs

LN90 EE20	Alesse LN 100/ 20EE	Lo-Estrin NA100 /20EE	Mircette DES0 150/EE20 10EE (days 24-28)	Cyclessa DESO 100/125/150 EE25	Ortho TriCyclen Lo/Norgest 180/215/250/ EE25	Nordette LN150 /EE30	Seasonale Ln150 EE30	YAZ 20Deso 20EE	Lo-Estrin/24 (6 months
3.10	1.1	0.75	1.11	1.08	2.67	0.44	1.98	1.42	1.79

For the lower dose estrogen/progestin oral contraceptives a Pearl index of less than or equal to 2 has been generally been accepted as the cut-off value above which it would be considered that efficacy in prevention of pregnancy has been established. In the days of higher dose combination contraceptive pills (30-35mcg EE and above) a Pearl index of less than 1 was required. The only approved extended cycle regimen drug, Seasonale had a PI of 1.98 presented in the summary **basis of approval. It is this reviewer's opinion** that 150 µg of LNG for Seasonale provides greater suppression of ovulation and leads to lower pregnancy rates than those seen with the 90µg LNG **in Lybrel™.**

In the forty five year history of approval of oral contraceptives only two products have been approved with a Pearl index greater than 2 (Estrostep®, PI=2.4 and Ortho-TriCyclenLo® PI 2.67). Clearly, these products represent ***outliers*** from the norm of acceptable efficacy. ***This reviewer believes that approvals of Estrostep™ and Ortho Tri-Cyclen™ OrthoNovum TriCyclen™Lo were not consistent with well-established policy within the division (HFD-510, later HFD-580) where a Pearl index >2 was considered too high for*** approval. In the early 1960s and 1970s a Pearl index of 1 was considered the norm. At an Advisory Committee meeting on October 3, 1975, with the review of Ovcon-35®, the Committee set a Pearl index of 1.5 as the highest level for approval. Estrostep was approved in 1996 (after receiving as non-approval in 1991) as a ***non***-de-novo oral contraceptive; it was a combination of two previously approved OCs and had the highest Pearl index (2.4) **until 2001 when Ortho Tri-Cyclen™Lo was approved.**

These two products are clearly outside the Pearl index for lower dose OCs and both had special reasons for approval that are inapplicable in the year 2006.

On February 26, 2006 Wyeth received a Discipline Review letter that outlined the Divisions concerns regarding NDA 21-864. In the letter the Division stated its concerns as the following:

- Additional pregnancies beyond those counted by the sponsor. These were 7 pregnancies that occurred either pre-therapy (2) or post therapy (5) that are previously outlined earlier in the review;
- The discontinuation rate of 56.8% is the highest rate the Division had reviewed in regards to a combination oral contraceptive; and
- Cycle control, in the form of sustained amenorrhea, is considered poor. Forty percent (40%) of subjects still had unanticipated bleeding in the form of bleeding or spotting at the end of one year of use.

The sponsor responded to the Division's letter on March 6, 2006. As a follow-up to the letter of March 6, 2006 the Division agreed to a face-to-face meeting with Wyeth on March 8, 2006. At this meeting Wyeth addressed the Division's concerns and provided additional supportive information. A significant amount of this information had not been previously provided to the Agency and was not available for review. At the March 8, 2006 meeting particular emphasis was placed on the documentation of the time period when subjects stopped their medication and when they became pregnant. The other 2 areas of concerns (discontinuations from the clinical trial and poor cycle control) were not fully discussed because of time constraints.

After the March 8 meeting, the sponsor provided the additional source documentation that was not contained in the original NDA. This source documentation was in several forms. The sponsor provided critical documentation in form of ultrasound documentation of early pregnancy for the purpose of dating some of the discrepant pregnancies, additional urine and quantitative hCGs, and correlation of the dates of pregnancy testing (hCGs) relative to the discontinuation of study drug. In addition information on the apparent mix-up of patient initials ——— that resulted in one patient being diagnosed as pregnant, when in fact it was another patient at the same office who was pregnant. The sponsor also provided supportive data on 2 subjects (313-067-5924, 313-091-8347) that suggest that the sponsor had done everything in their power to retrieve the test article (including certified letters requesting study participants to return the study drug). b(6)

Referring to Table 11 it is noted that in the sponsors ***original on therapy*** (≤1 4 days if post therapy treatment) efficacy evaluation in the 18-35 age group demonstrated 23 pregnancies with a Pearl index of 2.38 (1.51, 3.37); in the total population the Pearl index was 1.93 (1.23, 2.90). After review of the additional ***new*** source documentation ***this reviewer, in the current review cycle, is now in agreement that the total number of cycles is 12,572 and the total number of pregnancies is 23 which correlates with Pearl indices of 2.38 and 1.93 for the age up ≤ 35 and the total population, respectively. The corresponding Life table estimates at cycle 13 are 0.0348 (CI 0.0227, 0.0539) and 0.0297(CI 0.0183, 0.0435) for the ≤ 35 age group and the total population, respectively.***

As discussed previously for the lower dose estrogen/progestin oral contraceptives, a Pearl index of less than 2 has been generally accepted as the cut-off above which it would not be considered that effectiveness in prevention of pregnancy has been established. This value of a less than 2 Pearl index is documented by previous in-house reviews not disseminated (Products received non-approvals because of Pearl indices greater than 2.0). Per Contraceptive Technology 18th revised edition[1]) Table 19-1, the typical use provided estimated of the probabilities of pregnancy during the first year of typical use of each method in the US. For most methods, these estimates were derived from the experience of women in the 1995 National Surveys of Family Growth (NSFG), so that the information pertains to nationally representative samples of users. Pregnancy rates during typical use reflect how effective methods are for the average person who does not always use methods correctly or consistently.

In subjects using oral contraceptives the typical use percentage of women becoming pregnant was 8% and in subjects who had perfect use the percentage was 0.3%. Perfect use provides the best guess of the probabilities of method failure (pregnancy) during the first year of perfect use. A method is used perfectly when it is used **consistently with no missed pills or "make up"** multiple pill use[1].

In this clinical trial for Lybrel the perfect use Pearl index is 1.55 (CI 0.87, 2.56) in subjects age 35 years or younger. This is 5 times higher than that reported in Contraceptive Technology[1]. Importantly, the clinical trial pregnancy rates for both the less than or equal to age 35 population or the age group 18-49 population are the ***best that are likely to be achieved*** with this product. In addition most subjects in clinical trials who might have a problem are excluded within the inclusion/exclusion criteria (e.g. patients who might be on medication for antidepression/anxiety and antibiotic drugs). Furthermore, the built in clinical trial reminders (patient diary data, study visits and follow-up phone conversations) are not applicable to real life use. The perfect use Pearl index of 1.55, which is 5 times higher than the perfect use of combined oral contraceptives that is quoted by experts, suggests that this drug product, with its lower dosage of the progestin, is not successful at fully suppressing ovulation compared to previous higher dosage products (30μg-35μg). This may be contrasted with combined perfect use of condoms and spermicides (0.2%); this is the same percentage range as that achieved by the combined pill (0.3%) and the **IUD (Mirena™ [0.1%]) during perfect use**[1]. The central question to ask with this product in regards to efficacy is ***how low should the bar be lowered for the requirement to provide adequate protection to women who choose to cake OCs and believe that OCs are effective.*** Clearly other more effective products with similar safety profiles are already marketed. For this reviewer, an overall Pearl index of 2.38 associated with imperfect use (i.e. method/user failure) and a Pearl index of 1.55 (perfect use) is ***too high*** to assure women and their physicians that this method is effective. Additionally, the Life table analyses of **Lybrel™ suggest that the failure rate at 1 year** may be up to 5.39% for the age group 35 and under group.

The following table shows the number of additional pregnancies that occurred as the Pearl index increases, assuming there is a modest prescription market rate of ——— 28-day prescriptions: b(4)

Table 18. Additional Pregnancies Per Prescriptions as Pearl Index has Increased Over Time

Pearl Index	Number of Pregnancies
1.0	770
1.5	1,154
2.0	1,538
2.5	1,923
3.0	2,308
3.5	2,692
4.0	3,077

Note as Pearl index increases the total number of pregnancies will increased per each ——— market share of prescriptions written. For example, as of the end of 2005, the number one **prescribed OC was Yasmin™ with a market share of ——— . If Lybrel™ obtains a market** share of ———, prescriptions in the first year of use and the difference in the Pearl index is between 2.0 and 2.5, an additional 1,155 unanticipated pregnancies would occur in the US population. b(4)

If the discontinuation rate of study 0858A2-315-EU (33.1%) is combined with study 0858A2-313-NA over 13 months the overall discontinuation rate for Lybrel is decreased to 53.7%.

- Head-to-head studies were not performed therefore; results must be interpreted with caution.
- The Seasonal trial excluded subjects who had a history of greater than 10 consecutive days of bleeding and/or spotting while using OCs; Lybrel protocols permitted enrollment of these subjects.
- Different geographic regions of the country or countries may influence the withdrawal rate; shorter and smaller trials may also influence the withdrawal rate.
- Historical differences over time may affect parameters such as compliance or populations.

While the above bulleted items are indeed true, they do not explain away the high discontinuation rate associated with this product. This product has a high rate of discontinuation in the US population (higher than any previous product evaluated). Even when data is combined (I am in disagreement with combining efficacy in this instance) between US (56.8%) and European (33.1%) populations, the discontinuation rate is higher than has been seen with any previous product. Importantly, when reviewing the clinical trials history for the above previously stated similar products, no other product has as high a rate of discontinuation related ***directly to bleeding***. The sponsor compared products such as Mircette® and Seasonale® that had discontinuation rates in the 40%-47% range but neither product had overall discontinuations directly related to bleeding that approached 15%. In the Mircette® group a total of 107 patients discontinued at cycle 13; of this total 14/107 (7.76%) discontinued because of bleeding. In the

Seasonale® group 35/456 (13.0%) **discontinued at cycle 12 because of bleeding. Lybrel™** subjects had 363 (17%) discontinued due to an AE; of this total 181 (49.8%) discontinued because of a bleeding related AE. It is the opinion of this reviewer, when compared to the drug products that the sponsor has chosen as comparators discontinuations because of bleeding are substantially greater than what was reported in Mircette® or Seasonale® trials.

In the small comparative trial (315-EU) Loette (Alesse®) subjects were 3 times more likely to discontinue because of bleeding than subjects who took Lybrel. Combining data from these studies further accentuates the differences between the two study populations; they are different. The European population is less obese, more compliant and still had comparable discontinuation rates to the total US oral contraceptive population (30% range). As stated earlier, studies support the concept that increased discontinuation rates lead to unwanted pregnancies because subjects use no contraception or less effective contraception.

The sponsor has presented information on discontinuation rates with progestin only contraceptives and injectable progestin contraceptive to support the acceptability of the discontinuation rates for Lybrel. This reviewer does not agree with this approach and maintains while there is no other continuous use oral contraceptive, Seasonale remains the best comparator because it is an extended cycle (i.e. 90 days vs. 28-day cycle) regimen and has recently been approved (2003). There appears to be significant differences between these two extended/continuous methods and lesser discontinuations in Seasonale® patients support the hypothesis that the higher dosage of Seasonale® and a differing ratio of estrogen to progestin are contributing to a more balanced hormonal effect upon the endometrium. No comparable comparisons can be made between injectable progestin contraceptives or the progestin- only oral contraceptive.

Finally, with respect to the deficiency of poor cycle control, the sponsor responded with the following comments: Wyeth used the definitions adopted by the WHO as standard definitions. **The WHO definitions "may be more conservative"** than that used for several other OCs (e.g. Mircette). The sponsor used the following definitions for vaginal bleeding in the two studies:

- Bleeding;: sanitary protection was required;
- Spotting: some bleeding but no sanitary protection was required; and
- Amenorrhea: no bleeding or spotting during the period of interest.

This reviewer is not in agreement with the concept that the WHO standard definitions used by **Wyeth are "more conservative." In reviewing OCs** over the past 29 years WHO definitions have been the standard definitions used to describe bleeding, spotting and amenorrhea and in fact US definitions predate standard WHO definitions. Certain manufacturers have tried to combine certain elements of the basic definitions; subjects can bleed, spot or experience both in a menstrual cycle and this has historically been called intermenstrual bleeding or breakthrough bleeding or spotting with OC use.

The sponsor states that at cycle 13, 58.7% (505 of 860) subjects achieved amenorrhea at cycle 13. This figure is correct, but it does not take into account the total number of subject who started the study 2,048 and the substantial number who discontinued because of intermenstrual or

intracyclic bleeding. In addition combination pills can not be compared to progestin only OC because progestin-only OCs are prescribed to a different patient population. The progestin-only pills are prescribed to women who are breast feeding, cannot take OCs that have estrogen or women with fibroid tumors. In these instances these women are willing to accept lesser efficacy (97% efficacy rate) without the prolonged contraceptive effect of the injectable contraceptives because of indicated reasons. More importantly, the lesser efficacy of progestin-only pills is well known and well documented with physicians when they are compared to the pregnancy rates that approach a Pearl index of 2.5 for Lybrel.

In summary, the sponsor had submitted no data that would refute this reviewer contention that cycle control is poor with this product; when compared to similar lower dose OCs or the extended use OC Seasonale poor cycle remains a problem with Lybrel.

In conclusion, as a medical reviewer with a 25 year history of reviewing oral contraceptive products, I can not recommend approval of this product. The high overall Pearl index of 2.38 and the very high perfect use Pearl index of 1.55 in women aged 35 or less coupled with the high discontinuation rate of 56.8% and poor cycle control make this product unacceptable. Labeling *will not* educate patients nor clinicians that this drug is less effective than other lower dose products and I do not believe under the current class label that issues such as pregnancy rate, discontinuations, and cycles control can be illuminated to the degree that alerts the consumer and the clinician of less effectiveness of this product.

7 INTEGRATED REVIEW OF SAFETY

This safety database comprises a total of 2,533 subjects, including 18 subjects in a Phase 1 study (106-US), 58 subjects in a Phase 2 study (208-US), 2,457 subjects in Phase 3 studies (313-NA LNG 90µg/EE 20µg continuous-use regimen, and 318 subjects in a Phase 3 study (315-EU who received LNG and 315-EU) who received 100µg/EE 20µg in a 21-day regimen as a comparator. All studies were conducted in women at risk for pregnancy.

A total of 2,851 healthy women participated in the Phase 1, Phase 2, and two Phase 3 studies and received at least 1 dose of study medication. In the pooled Phase 3 studies, there were 22,171 cycles of exposure, and among those subjects who received continuous-use LNG 90µg/EE 20µg there were 1,137 subjects who completed 13 cycles of use. These parameters of drug exposure **exceed the Agency's requirement specified in the** Guidance for oral contraceptive development.

The following points summarize the most significant safety findings:

- Adverse events related to vaginal bleeding, including dysmenorrhea, metrorrhagia, and vaginal hemorrhage, were the most common treatment emergent adverse events (TEAEs). Other frequently occurring TEAEs included headache (migraine and not otherwise specified), nausea and abdominal pain.
- In the comparative study (EU315-EU) with the cyclic regimen, the overall incidence of adverse events related to vaginal bleeding was higher with the continuous-use regimen in

the first 6 pill packs, but not in the last 6 pill packs. In the Phase 3 clinical study 313-NA there were changes of -0.75g of hemoglobin at pill pack 7 that decreased to -.36g at post-treatment evaluation.

- There were 8 serious adverse events that were considered to be a least possibly related to **the LNG 90µg/EE 20µg continuous –use regimen.** These serious adverse events were consistent with those observed with other low dose oral contraceptives.
- Metrorrhagia and vaginal hemorrhage were the most common reasons for safety related discontinuations from the studies.
- Laboratory changes observed included increases in fasting blood glucose and lipids and are consistent with those observed with other low dose oral contraceptives.
- Body weight increases in these studies are not different between continuous use and cyclic regimen groups and are consistent with a population of women aged 18 to 49 years who use low dose oral contraceptives.
- Histologic changes in the endometrium in a subpopulation (n=146) showed no hyperplasia or malignancy; this is consistent with a decrease in endometrial growth and decidualization without atrophic endometrial changes.

7.1 Methods and Findings

The overall safety studies that evaluated the continuous use regimen of LNG 90µg/EE 20µg as an oral contraceptive included one Phase 1 study, 1 Phase 2 study, and two Phase 3 studies. The following table provides the complete study number, including the 0858A project prefix and country abbreviations for the suffixes. Studies were conducted in the United States, Canada, and Europe.

Table 19 The following table shows studies of LNG 90µg and EE 20µ in a Continuous Use in a 28-Day Regimen

Study CSR Number	Treatment Duration	Comparator
0858A2-106-US CSR-55147	28 days	None
0858A2-208-US CSR-50115	84 days	None
0858A2-313-NA CSR-55064	13 pill packs[a]	None
0858A2-315-EU CSR-55078	13 pill packs	13 pill packs (For each cycle: LNG 100 µg/EE 20 µg for 21 days, followed by 7 hormone-free days)

Abbreviations: LNG=levonorgestrel, EE=ethinyl estradiol, CSR=clinical study report, US=United States, NA=North America, and EU=Europe.
a. Thirteen (13) pill packs=12 months.

Table 20 The following table shows the Population Grouping for the Safety Database

Study	Treatment Group	Subjects, n
106-US	LNG 90 µg/EE 20 µg continuous use regimen	18
208-US	LNG 90 µg/EE 20 µg continuous use regimen	58
313-NA	LNG 90 µg/EE 20 µg continuous use regimen	2134
315-EU	LNG 90 µg/EE 20 µg continuous use regimen	323
	LNG 100 µg/EE 20 µg 21-day cyclic regimen	318
Totals		
LNG 90 µg/EE 20 µg continuous use regimen		2533
Comparator		318
All subjects		2851

Abbreviations: LNG=levonorgestrel, EE=ethinyl estradiol, US=United States, NA=North America, EU=Europe.
Sources: From synopses for studies 106 and 208 and section 8.1 of the CSRs for studies 313 and 315.

Note a total of 2,851 healthy women participated in the Phase 1, Phase 2, and Phase 3 trials and received at least one dose of study medication. In the ***pooled*** Phase 3 studies, there were 22,171 cycles of exposure and there were 1,137 subjects who completed 13 cycles of use.

7.1.1 Deaths

No deaths occurred during studies 106-US, 208-US, or 315EU. One (1) death occurred during study 313-NA. Subject 313-066-5864 had a normal screening physical examination and was diagnosed with an ovarian germ cell teratoma (stage 3) 6 months later. The subject was immediately withdrawn from the study and died 3 months later. Neither the investigator nor the medical monitor considered this death to be probably related to the administration of study drug. This reviewer is in agreement with this assessment.

7.1.2 Other Serious Adverse Events

In study 313-NA, 1 or more serious adverse events were experienced by 27 subjects; of this total, 7 events by 6 subjects were considered by the investigator and the medical monitor to be at least possibly related to study drug. The following table shows the 6 cases involved:

Table 21 Subjects with Serious Adverse Events at Least Possibly Related to Study Drug

Subject Number	Age	Adverse Event (COSTART) [a] Verbatim	Relationship	Severity	Onset
LNG 90 µg/EE 20 µg Continuous-Use Regimen					
313-025-1735	32	Pregnancy disorder Pregnancy, ectopic, left adnexal	Possibly	Mild	On-therapy
313-034-2606	37	Cholecystitis Cholecystitis	Possibly	Severe	On-therapy
313-067-5914 [b]	43	Vaginal hemorrhage Unexpected prolonged vaginal bleeding	Possibly	Moderate	Posttherapy
313-069-6101	31	Cholecystitis Calculus cholecystitis	Possibly	Moderate	On-therapy
313-070-6208	22	Deep thrombophlebitis Deep vein thrombosis	Definitely	Life-threatening	Posttherapy
		Pulmonary embolus Pulmonary emboli	Definitely	Life-threatening	Posttherapy
313-079-7129	44	Uterine fibroids enlarged Fibroid	Possibly	Severe	Posttherapy

a: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
b: Subject 313-067-5914 also had another serious adverse event categorized as "uterine fibroids enlarged," which was considered to be unrelated to study drug; see Table 10.3.1.2-2.

Note subject 313-070-6208 with the deep vein thrombosis and pulmonary embolus. This subject had been on subject medication for 321 days with documented extension from the leg to the lung. Also note 2 cases of cholecystitis that occurred after the subjects had been taking the study drug for 75 and 101 days; note that subject 313-06705914 had bleeding for 115 days (this subject

also had a history of uterine fibroids). Subject 313-079 was noted to have enlarging fibroids after 194 days of treatment with subject medication. The last subject was noted to have an ectopic pregnancy for which OCs (except triphasic OCs) have not be reported to have an increased incidence of this complication of pregnancy.

In summary table 2.1.3-1 an additional case (#313-061-5354) of DVT was reported. This subject history was confounded by being admitted to the hospital for severe asthma, obesity (126.3kg), cholelithiasis, and a mild case of renal stones. The subject was hospitalized several times and underwent 2 surgeries. At the time of discharge she was still in the study and was withdrawn the following day after surgery. This subject will be added to the total number of serious adverse events. This reviewer questions why this subject was entered into this trial because of multiple compounding factors. In addition 1 additional case of cholecystitis (#313-060-5203) should be added to the serious adverse events. This subject was ever entered into the study for 101 days. The subject is added after laparoscopic cholecystectomy confirmed chronic cholecystitis. Two additional cases of enlarged fibroids should be added (see summary table 2.1.3-1).

The sponsor also presents an additional 22 cases of subjects with serious adverse events that were considered unrelated to study drug in the opinion of the investigators. This reviewer is not in agreement with the opinion of the investigator **in a number of these cases. The sponsor's table** 10.3.1.2-2 will be shown below:

Table 22 Subjects with Serious Adverse Events At Least Possibly Related to Study Drug

Subject Number	Age	Adverse Event (COSTART)[a] Verbatim	Relationship	Severity	Onset
LNG 90 µg/EE 20 µg Continuous-Use Regimen					
313-001-8552	30	Pyelonephritis Pyelonephritis (right)	Definitely not	Severe	On-therapy
313-001-8591	22	Pyelonephritis Right pyelonephritis	Definitely not	Severe	On-therapy
313-011-0309	41	Uterine fibroids enlarged Uterine fibroids	Probably not	Moderate	On-therapy
313-011-0323	27	Abortion Miscarriage	Definitely not	Moderate	Posttherapy
313-017-0917	24	Gastritis Gastritis	Probably not	Severe	Posttherapy
313-033-2508b[b]	22	Biliary pain Gall bladder attack	Probably not	Severe	On-therapy
313-033-2531	35	Infection *E coli* infection (gastrointestinal)	Definitely not	Severe	On-therapy
		Urinary tract infection Urinary tract infection	Definitely not	Severe	On-therapy
		Sepsis Urosepsis	Definitely not	Moderate	On-therapy
		Pyelonephritis Pyelonephritis	Definitely not	Severe	On-therapy
		Vomiting Vomiting	Definitely not	Moderate	On-therapy
		Dehydration Severe dehydration	Definitely not	Severe	On-therapy
		Dyspnea Dyspnea	Probably not	Mild	On-therapy
313-038-3019	40	Accidental injury Left ankle trimalleolar fracture	Definitely not	Severe	On-therapy

Table 21 continued

Subject Number	Age	Adverse Event (COSTART)[a] Verbatim	Relationship	Severity	Onset
313-052-4429	19	Anxiety Situational anxiety	Definitely not	Mild	On-therapy
313-054-4634	34	Abdominal syndrome acute Appendicitis	Definitely not	Severe	Posttherapy
313-058-5049	21	Depression Worsening of depression	Definitely not	Severe	Posttherapy
313-059-5101	24	Cholecystitis Cholecystitis	Probably not	Severe	On-therapy
313-060-5203b[b]	30	Gastrointestinal disorder Malfunctioning gallbladder (unknown)	Probably not	Moderate	On-therapy
313-061-5354	32	Abdominal pain Right lower quadrant pain	Probably not	Severe	On-therapy
		Fever Intermittent fever	Definitely not	Mild	On-therapy
		Abdominal pain Abdominal pain	Probably not	Moderate	On-therapy
		Asthma Asthma exacerbation	Definitely not	Moderate	On-therapy
		Gastrointestinal disorder Biliary dyskinesia	Definitely not	Moderate	On-therapy
		Deep thrombophlebitis Left lower extremity deep vein thrombosis	Definitely not	Moderate	On-therapy
		Asthma Asthma exacerbation	Definitely not	Moderate	On-therapy
313-064-5601	20	Abdominal pain Abdominal pain in upper right quadrant	Definitely not	Severe	On-therapy
		Pneumonia Pneumonia	Definitely not	Severe	Posttherapy
313-064-5613	27	Depression Severe depression (with suicidal ideation)	Definitely not	Severe	Posttherapy
		Suicidal ideation (Severe depression with suicidal ideation)	Definitely not	Severe	Posttherapy
313-066-5864	21	Neoplasm	Probably not	Severe	On-therapy

Table 21 continued

Subject Number	Age	Adverse Event (COSTART)[a] Verbatim	Relationship	Severity	Onset
		Immature teratoma stage 3			
313-067-5914 [c]	43	Uterine fibroids enlarged Uterine fibroids	Probably not	Moderate	Posttherapy
313-077-6903	29	Convulsion Seizures	Probably not	Severe	On-therapy
313-079-7111	32	Back pain Back pain	Definitely not	Severe	On-therapy
313-080-7229	37	Gastritis Gastritis	Probably not	Severe	On-therapy
		Stomach ulcer Gastric ulcer	Probably not	Severe	On-therapy
313-086-7857	33	Skin disorder Right arm lesion	Probably not	Severe	On-therapy

a: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
b: In the opinion of the medical monitor, the relationship of the serious adverse event to study drug was considered to be possibly related to study drug. Because the assignment of relationship differed from that of the investigator, the more conservative of the relationships was reported in the subject narrative.
c: Subject 313-067-5914 also had another serious adverse event categorized as "vaginal hemorrhage", which was considered to be related to study drug; see Table 10.3.1.2-1.

Upon review of cases report forms (CRF) this reviewer is in disagreement with the opinion of the investigator in a number of these cases. Case numbers 313-011-0309, 313-017-0917, 313-033-2508, 313-033-2531 (previously presented), 313-059-5101 and 313-060-5303[b] (previously discussed), 313-061-5354 (previously discussed), 313-067-5914 are ***probably*** associated with use of study drug and these conditions have been reported in other OC studies. Subjects 313-058-5049, 313-064-5613 are ***possibly*** associated with study drug and have been reported in other OC studies.

7.1.3 Dropouts and Other Significant Adverse Events

In the safety efficacy database of 2,134 subjects, a total of 362 subjects (17%) had adverse events that were reported as the primary reason for discontinuation of study drug. Of these events, vaginal hemorrhage 78 (3.7%), metorrhagia 74 (3.5%) and emotional lability 26 (1.2%) were the most common according to the sponsor.

Reviewer's Comment:
The number of bleeding sub-diagnosis under COSTART is somewhat misleading. Review of the following table 20 (sponsor's table 10-3.1.3-1) under urogenital system shows that 181/362 subjects discontinued from the study because of some type of urogenital bleeding.

Table 23 Number of Subjects Reporting Adverse Events as the Primary Reason for Discontinuation of Study Drug

Body System Adverse Event Any Adverse Event	LNG 90 µg/EE 20 µg Continuous-Use Regimen (n = 2134) 362 (17.0)[a]
Body as a Whole	
Abdominal pain	3 (0.1)
Back pain	2 (0.1)
Generalized edema	1 (0.0)
Headache	14 (0.7)
Hernia	1 (0.0)
Neoplasm	1 (0.0)
Pain	1 (0.0)
Pelvic pain	2 (0.1)
Cardiovascular	
Deep thrombophlebitis	2 (0.1)
Hypertension	6 (0.3)
Migraine	13 (0.6)
Palpitation	1 (0.0)
Peripheral vascular disorder	1 (0.0)
Phlebitis	1 (0.0)
Digestive	
Abdominal distension	1 (0.0)
Cholecystitis	1 (0.0)
Gastritis	1 (0.0)
Liver function tests abnormal	2 (0.1)
Nausea	7 (0.3)
Tongue edema	1 (0.0)
Vomiting	3 (0.1)
Endocrine	
Endocrine disorder	1 (0.0)
Goiter	1 (0.0)
Hypothyroidism	1 (0.0)
Hemic and Lymphatic	
Antinuclear antibody present	1 (0.0)
Metabolic and Nutritional	
Hypercholesteremia	1 (0.0)
Hyperlipemia	1 (0.0)
Weight gain	20 (0.9)
Musculoskeletal	

Table 22 continued

Body System Adverse Event	LNG 90 µg/EE 20 µg Continuous-Use Regimen (n = 2134)
Leg cramps	1 (0.0)
Fibromyalgia	1 (0.0)
Nervous	
Anxiety	3 (0.1)
Carpal tunnel syndrome	1 (0.0)
Convulsion	1 (0.0)
Depression	7 (0.3)
Emotional lability	26 (1.2)
Hostility	3 (0.1)
Libido decreased	2 (0.1)
Manic depressive reaction	1 (0.0)
Paresis	1 (0.0)
Somnolence	1 (0.0)
Skin and Appendages	
Acne	6 (0.3)
Alopecia	2 (0.1)
Hair disorder	1 (0.0)
Maculopapular rash	1 (0.0)
Night sweats	1 (0.0)
Rash	2 (0.1)
Urticaria	1 (0.0)
Urogenital	
Breast disorder	1 (0.0)
Breast enlargement	2 (0.1)
Breast neoplasm	2 (0.1)
Breast pain	4 (0.2)
Cervix disorder	1 (0.0)
Dysmenorrhea	4 (0.2)
Menorrhagia	12 (0.6)
Menstrual disorder	6 (0.3)
Metrorrhagia	74 (3.5)
Pyelonephritis	1 (0.0)
Urinary tract disorder	1 (0.0)
Uterine fibroids enlarged	6 (0.3)
Uterine hemorrhage	11 (0.5)
Uterine spasm	1 (0.0)
Vaginal hemorrhage	78 (3.7)
Vaginal moniliasis	2 (0.1)
Vulvovaginal disorder	2 (0.1)
Terms Not Classifiable	
Reaction unevaluable	1 (0.0)

Note that under body system, the 2 most prominent body systems leading to discontinuation of this oral contraceptive were cardiovascular system and the urogenital system. Note that there were 2 case of DVT and that there were 13 cases of migraine that are additive to 14 cases of generalized headache. Under Urogenital system, note that there were 12 cases of menorrhagia, 6 cases of menstrual disorder, 74 cases of metorrhagia, 6 cases of uterine enlarged, 11 cases of uterine hemorrhage, and 78 cases of vaginal hemorrhage. Taking into account only the urogenital system 181/362 (50%) of subjects discontinued use of this OC with bleeding related adverse

events. This appears to be very high considering that a continuous-use OC was designed to decrease overall bleeding and not lead to the subject discontinuing its use because of bleeding.

1.3.1 Overall profile of dropouts
The overall profile of discontinued subjects is fairly consistent with other studies for OCs. Refer **to reviewer's table 4 (sponsor's table 8.1.1-1).** Again note 1,213 (56.8%) of subjects were unable to continue use of this OC. Of the reasons for discontinuance, note the highest percentage was due to an adverse event 363 (17%), 336 (15.7%) was subject request, 223 (10.4%) was lost to follow-up and 102 (4.8%) were discontinued by the investigator.

7.1.3.2 Adverse events associated with dropouts

As previously stated, most subjects who discontinued from the study reported some type of bleeding associated with the OC. Note the highest number of subjects had vaginal hemorrhage, followed by metrorrhagia, which reflects breakthrough bleeding and spotting rather than heavy withdrawal bleeding. Note that emotional lability, weight gain, migraine and headache are less than 2% for each individual symptom.

7.1.3.3 Other significant adverse events

There are no significant adverse events that are not consistent with the use of a low-dose oral contraceptive.

7.1.4 Other Search Strategies

For the overall review of this electronic NDA, recently approved (since 2001) oral contraceptives were compared ***(cross-study)*** for both safety and efficacy. This product was compared to a traditional 21day on 7 day off OC Alesse® as well as a similar continuous use OC Seasonal, in which the subject ingest the OC for 84 days with 7 days off the pill. Since no statistical inferences can be made, comparisons will be made based on percentages in the respective trials.

7.1.5 Common Adverse Events

In review table 19 (sponsor's table 10.2.2.1-1) it is noteworthy that *640 (30%) of subjects were noted to have a headache.* This appears ***higher*** than other studies with levonorgestrel. The etiology of this high rate of headache can only be speculative. The lack of the 7 day hormone free period could be involved. The number of subjects with dysmenorrhea 419 (19.6%) also appears higher than other lower dose OCs. Again note vaginal hemorrhage and metrorrhagia with 7.1% and 6.2% of subjects reporting these urogenital symptoms. Nausea is reported in 276 (12.9%) of subjects which is slightly higher than most lower dose OCs; abdominal pain, back pain, infection, pain, and URI noted to be similar to other studies of lower dose OCs.

7.1.5.1 Eliciting adverse events data in the development program

No unusual or unexpected adverse events were noted in the developmental program for this OC.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse event categorization and preferred terms such as COSTART and TEAE are consistent with the long history of reporting adverse events with OCs.

7.1.5.3 Incidence of common adverse events

See section 7.1.5

7.1.5.4 Common adverse event table

Table 24 The following table shows the number (%) of subjects in the total population with treatment emergent adverse events (Reported by ≥ 5% of subjects) Sponsor's Table 10.2.2.1-1

Body System Adverse Event (COSTART)[a]	LNG 90 µg/EE 20 µg Continuous-Use Regimen (n = 2134)
Any Adverse Event	1857 (87.0)
Body as a Whole	
Abdominal pain	204 (9.6)
Accidental injury	131 (6.1)
Back pain	213 (10.0)
Flu syndrome	172 (8.1)
Headache	640 (30.0)
Infection	196 (9.2)
Pain	192 (9.0)
Digestive	
Diarrhea	128 (6.0)
Nausea	276 (12.9)
Respiratory	
Pharyngitis	224 (10.5)
Rhinitis	142 (6.7)
Sinusitis	140 (6.6)
Upper respiratory infection	351 (16.4)
Skin and Appendages	
Acne	135 (6.3)
Urogenital	
Breast pain	146 (6.8)
Dysmenorrhea	419 (19.6)
Metrorrhagia	132 (6.2)
Vaginal hemorrhage	152 (7.1)
Vaginal moniliasis	149 (7.0)
Vaginitis	124 (5.8)

a: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

7.1.5.5 Identifying common and drug-related adverse events

Common and drug related adverse events were compared to ethinyl estradiol and levonorgestrel OCs and a similar continuous use OC. Results with most AEs are comparable.

7.1.5.6 Additional analyses and explorations

Additional analyses were conducted and compared to low dose OC and the one approved continuous use OC Seasonique®.

7.1.6 Less Common Adverse Events

There were no unusual less common adverse events reported such as increase breast pain, tenderness, fluid retention, etc.

7.1.7 Laboratory Findings

Forty-two (42) subjects were considered to have clinically important laboratory changes. Of these subjects, 37 had changes in the laboratory measures typically affected by OCs, i.e. fasting blood glucose, fasting lipids, hemoglobin, and hematocrit; 4 had changes in liver function test; 2 subjects in the endometrial histology sub-study had changes in hemostasis measures that were considered to be clinically important.

Fasting Blood Glucose Levels (FBS)
Five subjects had increases in fasting blood glucose levels that were considered to be clinically important based on the diagnostic criteria used by the American Diabetes Association for hyperglycemia. According to this criterion, a fasting blood glucose value greater than 126 mg/dL is indicative of hyperglycemia. The increases seen in all 5 subjects were greater than 25% from baseline and were greater than 126 mg/dL at the last observation. None of these subjects discontinued study drug or withdrew from the study as a result of these changes, although 3/5 (313-003-8757, 313-014-0625,313-039-3161) Type-2 diabetics had to have their insulin treatment modified.

The baseline and mean change over time for fasting blood glucose levels were calculated. Statistically significant ($p < 0.05$) increases were observed in the mean change in fasting blood glucose levels during pill pack 7 (0.17 ± 0.64 mmol/L)) and post-treatment evaluation (0.14 ± 0.56 mmol/L). These changes were not considered clinically important.

Fasting Lipid Parameters
Twenty-eight (28) subjects had increased in fasting lipid parameters that were considered to be clinically important based on diagnostic criteria included in the National Cholesterol Education **Program treatment Panel III (ATP) for "high"** values in total cholesterol, LDL-C and triglycerides. The criteria used to evaluate the observed decreases in HDL-C were based on the **ATP III diagnostic criteria for "low" values** in HDL-C. Based on these classifications, the

changes observed in the fasting lipid values for these 28 subjects were all considered to be clinically important. (See Table below)

Table 25 Subjects with Clinically Important Changes in Fasting Lipid Parameters Sponsor's Table 10.4.1.1.2-1

Triglycerides	HDL-C	LDL-C	TotalCholesterol
313-001-8552	313-030-2206	313-010-0202	313-031-2326
313-001-8590	313-054-4621	313-031-2326	
313-002-8605	313-066-5856		
313-008-0010	313-066-5864		
313-032-2404	313-073-6516		
313-033-2525	313-075-6705		
313-033-2531	313-084-7618		
313-034-2616	313-087-7916		
313-047-3903			
313-047-3922			
313-050-4246			
313-051-4306			
313-052-4416			
313-062-5423			
313-068-6003			
313-079-7116			
313-095-9401			
313-095-9417			

Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

The observed increase in total cholesterol (n=1), LDL-C (n=2), and triglycerides (n=18) were equivalent to an increase from the midpoint of the normal range to the high ATP III value; the last observed values for these subjects were all above the high ATP III value. The observed decrease in HDL-C (n=8) was > 10 mg/dL from baseline to < 40mg/dL (ATP III low value at the last observation, with a decrease in the HDL-C/total cholesterol ratio >20%. None of these subjects discontinued study drug because of lipid changes.

The baseline mean and mean change over time in fasting total cholesterol, HDL-C, LDL-C, and triglyceride levels were calculated. During pill pack 7 the post-treatment evaluation, a significant ($p < 0.05$) increase was observed in the mean change in fasting total cholesterol 0.063±0.614mmol/L), LDL-C (0.085 mmol/L), and triglycerides (0.14023± 0.46317 mmol/L); a significant ($p < 0.05$) decrease was observed in HDL-C (-0.026±0.226 mmol/L). Similar changes were also shown for post-treatment levels of total cholesterol, HDL-C, LDL-C, and triglycerides.

Liver Function Tests
The changes in the liver function test for 5 subjects were considered to be clinically important. These subjects (313-030-2290, 313-039-3111, 313-062-5403, 313-070-6239, 313-011-0320) had normal values of AST at baseline, had increases that were greater than 2-fold above the upper limit of normal at the last observation. Subject 313-070-6239 discontinued study drug because of her elevated AST.

Hemoglobin and Hematocrit

Four (4) subjects had changes in their hemoglobin or hematocrit that were considered to be clinically important. These 4 subjects (313-026-1820, 313-028-2031, 313-066-5864, 313-091-8341) had decreases in hemoglobin or hematocrit of greater than 10% from baseline to less than 10g/dL (less than 100g/L) or had decreased of greater than 20% from baseline at the last observation. There were no discontinuations from the study because of decreases in hemoglobin.

The baseline mean and mean change over time in hemoglobin and hematocrit levels were calculated. During pill pack 7 a significant ($p < 0.001$) decrease from baseline in hemoglobin was reported. There is a mean difference of -0.75(±7.14g/L). By the post-treatment evaluation, mean hemoglobin -0.36(±7.93g/L) was ***not significantly*** different from baseline, but ***lower*** than baseline supporting the view that subjects were bleeding throughout this study.

Endometrial Histology Sub-study Hemostasis Measures

Two (2) subjects had potentially clinically important changes in their hemostasis measures. Subject 313-004-8801 had a greater than 3-fold increase from baseline prothrombin fragment F1 +2 and D-dimer at the post-treatment evaluation. There were no clinical manifestations of this finding. Subject 313-058-5074 had factor V Leiden C heterozygous for mutation at baseline. This subject had a transitory decrease in Protein C and Protein S activities in pill pack 7 that returned to baseline during pill pack 13; there were no meaningful change in protein C or Protein S antigen levels.

Cervical Cytology over Time
There were 5 subjects (313-008-002, 313-058-5050, 313-076-6824, 313-043-3532, 313-056-4809) who developed high grade squamous intraepithelial lesions (SIL) that were considered clinically important. Subject 313-008-002 was discontinued from the study on December 2, 2003 after being in the study 183 days. She had an initial pap smear that was normal; on [redacted] a Pap smear that was read as HSIL with HPV, subsequent follow-up on [redacted] revealed an LSIL lesion with HPV. Subject 313-058-5059 completed the study after 190 days. She has abnormal Pap smear on [redacted] that reveled HSIL. On [redacted] and endocervical curettage (ECC) and ectocervical biopsy revealed no dysplasia. Subject 313-076-6824 completed the study after 204 days. A Pap smear on [redacted] revealed HSIL. On [redacted] the results of a colposcopy were reported as negative. Biopsy results revealed chronic cervicitis with squamous metaplasia and no evidence of dysplasia. Subject 313-043-3532 completed the study. She had an abnormal Pap smear on [redacted] that revealed HGIL. The patient has a colposcopy (date unknown to the investigator) and had a loop electrocautery excision procedure (LEEP). The results are unavailable to the investigator. Subject 313-056-4809 completed the study (368 days). She had an abnormal Pap smear on [redacted]. An ECC and cervical biopsy [redacted] revealed a low grade squamous intraepithelial lesion (CIN 1). Additional follow-up on [redacted] revealed that the specimen was negative for CIN or malignancy.

b(6)

Reviewer's Comment
The 5 cases of high grade SIL were, in the opinion of this reviewer, appropriately followed and managed. The only subject with significant surgery was the subject with the LEEP procedure. Unfortunately, the results of the LEEP procedure are not available for review.

Table 26 Summary of Cervical Cytology Data: Number (%) of Subjects Sponsor's Table 10.5.4.2.

Finding	Screening (n=2123)	Pill Pack 7 (n=1187)	Posttreatment (n=1112)
Satisfactory for evaluation	2122 (100)	1179 (99)	1089 (98)
Negative for intraepithelial lesion or malignancy	2121 (100)	1093 (92)	1002 (90)
Epithelial cell abnormalities—glandular cell (total)	0	1 (<1)	3 (<1)
Atypical glandular cells, not otherwise specified		1 (<1)	1 (<1)
Atypical endocervical cells, not otherwise specified		0	2 (<1)
Epithelial cell abnormalities—squamous cell (total)	1 (<1)	85 (7)	84 (8)
Atypical squamous cells of undetermined significance	1 (<1)	53 (4)	64 (6)
Atypical squamous cells, cannot exclude high-grade SIL	0	3 (<1)	4 (<1)
Low-grade SIL	0	26 (2)	14 (1)
High-grade SIL	0	3 (<1)	2 (<1)

Abbreviations: SIL = squamous intraepithelial lesion.
Source: From CYTO4

Note the number of epithelial cell abnormalities at pill pack 7 and post-treatment. Overall, the number of epithelial abnormalities at pack 7 is 7% and post treatment 8%. Also note of this total 6% are atypical squamous cells of undetermined significance. These numbers are consistent with atypical cell types seen in other OC studies.

7.1.7.1 Overview of laboratory testing in the development program
Clinical laboratory evaluations for the assessment of safety in the total population were to be performed before treatment, during pill pack 7, and after treatment. To maximize uniformity, each laboratory test was performed at a single laboratory. All laboratory data were examined to identify individuals who had laboratory values of potential importance.

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

Laboratory tests of potential clinical importance were identified by the medical monitor and defined in the Statistical Analysis Plan. The investigator and the medical monitor reviewed all abnormal laboratory values.

7.1.7.3 Standard analyses and explorations of laboratory data

See previous discussions relating to fasting blood sugar, fasting lipids, hemoglobin and hematocrit, changes in liver function, changes in endometrial histology and changes relating to cytology.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

See previous discussions relating to fasting blood sugar, fasting lipids, hemoglobin and hematocrit, changes in liver function, changes in endometrial histology and changes relating to cytology.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

See previous discussions relating to fasting blood sugar, fasting lipids, hemoglobin and hematocrit, changes in liver function, changes in endometrial histology and changes relating to cytology.

7.1.7.4 Additional analyses and explorations

The sponsor devoted significant resources to a 3-month cycle related symptom sub-study (CRSS). Subjects recruited to this sub-study must have been pre-qualified by having a history of dysmenorrhea or symptoms of premenstrual syndrome (PMS) and must have met the study definition of cycle-related symptoms with data collected prospectively by mean of a questionnaire (17-item Penn Daily Symptom Report [DSR] which included a Likert scale to evaluate the severity of symptoms.

To become eligible for the CRSS, subjects had to keep a daily of symptoms scores for 1 cycle and to meet enrollment requirements for at least 1 or 3 subgroups of the CRSS: PMS, cyclic symptoms, and dysmenorrhea. The entry criteria for each subgroup are summarized below:

- PMS subgroup: For each subject, the total score on the 17-item Penn DSR scale must have been ≤ 40 for the postmenstrual days (days 6 to 11) and ≥ 80 for the premenstrual days (I.e. the last 6 days of the baseline cycle, days 23 to 28).
- Cyclic symptoms subgroup: Each subject must have had at least 2 symptoms on the 17-item Penn DSR scale rated ≥ 2 for at least 2 days during the premenstrual days of the baseline screening cycle. In addition, the total score on the 17-item Penn DSR scale must have been ≤ 30 for the postmenstrual days and between 50 and 79, inclusive, for the premenstrual days.
- Dysmenorrhea sub-group: A subject must have had at least 1 day rated ≥ 3 **for "cramps" or rated 2 for "cramps" during days 1 to** 5 of the menstrual cycle, plus ingestion of medication for cramps on that day.

The PMS subgroup had 78 subjects who met the criteria for symptoms. In this small subgroup the mean total premenstrual score decreased from 143.7 to 60.6 at cycle 1, and decreased further in pill packs 2 and 3. In the cyclic symptoms sub-group, 36 subjects met the criteria for the cyclic symptoms subgroup at baseline. The total premenstrual score was reduced from 63.2 to 28.0 for at least 9 of the individual items. The total postmenstrual score increased from baseline to pill pack 1 by 11.3 and remained at this level in pill packs 2 and 3. A total of 259 subjects met the baseline criteria for entry into the dysmenorrhea subgroup. Cramps were analyzed during the first 5days of the baseline cycle or pill pack interval. The mean cramp score decreased slightly in pill pack 1 and decreased further in pill packs 2 and 3. Data analyzed by the sponsor at this time appears encouraging but can ***only be considered exploratory at this time.***

.1.7.5 Special assessments

No special assessments are reported in this study other than the CRSS and PMS related data.

7.1.8 Vital Signs

Blood Pressure
There were 11 subjects who were identified as having changes of potential importance in vital signs; 4 subjects (313-015-0710, 313-061-5356, 313-067-5969, 313-098-9706) were considered to have clinically important changes in blood pressure and 7 subjects (313-010-0211, 313-028-2002, 313-030-2236, 313-061-5335, 313-061-5341, 313-074-6630, 313-076-6832) had clinically important changes in body weight. The changes in blood pressure involved a ***nontransitory*** increase in diastolic blood pressure to > 100mm Hg or an increase in systolic blood pressure > 160 mmHg. Seven (7) subjects had a ***nontransitory*** weight gain from baseline of greater than 20%. None of these subjects discontinued from the study because of weight gain.

A significant ($p > 0.001$) increase from baseline in mean systolic and diastolic blood pressure was seen during pill pack 3, pill pack 7, and pill pack 10. The mean systolic change was 0.36 mmHg at pill pack 3, 1.15 mmHg at pill pack 7, 1.48 mmHg at pill pack 10 and 0.94 mmHg at the post-treatment visit. The mean increases in diastolic blood pressure were also significant at pill pack 3, pill pack 7, pill pack 10 and post-treatment ($p<0.001$). The mean diastolic change was 0.84mg Hg, 1.85mmHg, 1.81mmHg and 1.85mgHg at pill packs 3, 7, 10, and post-treatment respectively. Although these changes are statistically significant, overall changes of 1-2mmHg over a 1 year period are not clinically significant.

Body Weight
At pretreatment the mean body weight for all subjects was 70.25kg. Over the treatment period was a statistically significant increase in body weight of .76kg (1.67lbs). The increase weight gain occurred throughout the treatment period, 0.34kg at pill pack 3, 0.47kg at pill pack 7, 0.82 at pill pack 10 and 0.76kg at the post-treatment visit. An overall weight gain of <2 pounds would be acceptable to most women in a one year treatment period and is not, in the opinion of this reviewer, clinically significant.

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

Comments are made in other sections of this review, regarding the use of this extended regimen and that of Seasonale the previously approved extended use oral contraceptive.

7.1.8.4 Additional analyses and explorations

Additional analyses will be made regarding the pregnancy rates of the sponsor and cycle control, and discontinuations in this study

7.1.9 Electrocardiograms (ECGs)

No EKGs were performed in this study.

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

Study 0858A2-313NA will be compared to study 0858A2-315EU in Europe that compared Lybrel to Alesse®, a 21-day 7 day placebo use oral contraceptive marketed by the sponsor. In addition —— will be compared in relationship to pregnancy rate, cycle control and bleeding to Seasonale® the previously approved extended use oral contraceptive b(4)

7.1.10 Immunogenicity

There was no special immunogenicity studies performed with this product.

7.1.11 Human Carcinogenicity

There was no special carcinogenicity studies performed with this product.

7.1.12 Special Safety Studies

Mean changes in Hemostasis Measures
Hemostasis measures were assessed before treatment, during pill pack 7 and pill pack 13, and after treatment to measure factor V Leiden (at baseline only), antithrombin III activity, protein S antigen, protein S activity, protein c antigen, and protein C activity (pretreatment, and at visits 1B, 3, and 4A). Results (Table 15.5.4.1.2-1 not reproduced) show a significant increase in the mean change in protein C and Protein C activity, factor VII antigen, and protein S free antigen during pill pack 7; a significant decrease was observed for prothrombin time. During pill pack 13, a significant increase in the mean values for factor VII antigen and for protein S free antigen was observed. No significant changes were observed in any of the hemostasis measures at the post-treatment evaluation.

Reviewer's Comment:
This is consistent with studies of other OCs especially those that utilize an ethinyl estradiol and levonorgestrel combination. The lower dose of E/P did not appear to confer any hemostatic benefit nor any changes that could be viewed as deleterious when compared to the 30μg EE/levonorgestrel pills.

Endometrial Biopsy Findings
Fifty-six (56) subjects were entered into the endometrial biopsy sub study. Results were compared before treatment to the last to the last on-therapy visit beyond pill pack 6. At baseline 56 (60%) of subjects had findings classified as **"weakly/proliferative endometrium." At the last** on therapy visit, more subjects had secretory endometrium than baseline and additional subjects **had "other" for a diagnosis. Subjects with the "other diagnosis had a histologic diagnosis that**

included "inactive", and/or "benign"endometrium (n=42) and proliferative endometrium or a few proliferative glands.

Reviewer's Comment:
The above biopsy findings are consistent with what would be expected of a low dose oral contraceptive in women in the reproductive age category and show no evidence of an estrogenic effect upon the endometrium. As expected, there were no cases of hyperplasia or malignancy.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This oral contraceptive has no withdrawal or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

Oral contraceptives have a well-documented effect upon human reproduction and the pregnancy rate that is well documented in over 45- years of use.

7.1.16 Overdose Experience

There were no reported overdoses in this study. Adverse events relating to an overdose of an oral contraceptive are well documented in the class label for oral contraceptives.

7.1.17 Postmarketing Experience

There has been no postmarketing experience with this oral contraceptive. Data presented with this NDA suggest that there will be a greater number of unscheduled days of unexpected bleeding and more women will stop using this product because of unexpected bleeding.

7.2 Adequacy of Patient Exposure and Safety Assessments

This study has more than the required exposures of 200 women taking this product for one year or 13 cycles. A total of 2,134 subjects took at least 1 dose of study drug. This is more than adequate to characterize safety assessments relating to this low dose oral contraceptive that is very similar to Alesse® except for 10mcg per day less of levonorgestrel and continuous use rather than the standard 21 days of use followed by 7 days of placebo.

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

The safety database for Study Drug comprises a total of 2,533 subjects, including 18 in a Phase 1 study (106-US), 58 subjects in a Phase 2 study (208-US), 2,457 subjects in Phase 3 studies (313-NA) and 315-EU) who received in a continuous use regimen, and 318 subjects in a Phase 3 study (315-EU) who received LNG 100µg/EE 20µg in a 21-day cyclic regimen as a comparator. The total number of subjects is 2,851. In the pooled phase 3 studies, there were 22,751 cycles of

exposure, and among those subjects who received continuous use LNG 90µg/EE 20µg, 1,137 subjects completed 13 cycles of use.

7.2.1.1 Study type and design/patient enumeration

This study (0858A2-313-NA) was a Phase 3, single treatment, multicenter, open label study for the safety and contraceptive efficacy of an OC containing a combination of LNG 90µg/EE 20µg in a continuous-use regimen (dispensed as 28 day pill packs). Patients in this study had a 10-digit identification code that began with 313.

7.2.1.2 Demographics

The demographic and baseline characteristics were summarized in Table 8.2.1-1. This table (not reproduced) revealed that for the total study population of 2,134 subjects 1646 (77.13%) were white, 217 (10.17%) were black, 188 (8.81%) were Hispanic, 33 (1.55%) were Asian, and 50 (2.34%) were described as other. The mean age was 28.77 years. The mean height was 164.39 ± 666 cm. the mean weight was 70.38±16.83 kg and the Body mass index was 26.04±6.07. Additionally, 911 (42.69%) of subjects had no pregnancies, 465 (21.79) were nulliparous, 399 (18.70%) had two previous pregnancies, 205 (9.61%) had been pregnant three times, 91 (4.26%) had been pregnant 4 times, 40 (1.87%) had been pregnant 5 times, and an additional 23 subjects had been pregnant from 6-11 times. There were 1694 (79.38%) subjects who were non-smokers and 440 (20.62) who were smokers. In the smoking group subject smoked on average 7.54 cigarettes per day. Subjects on average had 14.59 ± 2.27 years of education. Subjects were reported have been on study drug 237.26 ±129.25days and 1,023 (58.06) subjects did not complete the study while 921 (43.16%) completed the study.

Of the 2,134 subjects in the total population, 1,762 were aged 35 years or younger at the time of enrollment. These subjects had demographic and baseline characteristics (i.e. race, height, weight, BMI, and previous pregnancies) similar to those to the total population, but were younger with a mean age of 26.43 years; there were more nulliparous subjects in the <35 age group were 47.33% vs. 42.69%, otherwise the groups were very similar.

7.2.1.3 Extent of exposure (dose/duration)

A total of 18,710 pill packs were reported for the 2,134 subjects in the total study population. Of the total number of pill packs reported, 15,461 (83%) were included in the Pearl index analyses and 11,295 (60%) were included in the Life table analyses for contraceptive efficacy. Data from 3,249 pill packs were excluded from the Pearl Index and 7415 were excluded from the life table analyses of contraceptive efficacy in the total population because the pill packs met 1 or more reasons for exclusion.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary data sources were used in the comparative trial 0858A2-315-NA to evaluate efficacy and safety of LNG 90µg/EE 20µg compared to LNG 100µg/EE 20µg over 13 cycles of use.

Additionally, cycle control and bleeding profiles were compared to Seasonale® (LNG 150µg/EE 30µg) that is given for 84 days followed by 7 pill free days.

7.2.2.2 Postmarketing experience

There has been no postmarketing experience with this product.

7.2.2.3 Literature

There was no additional literature review with this product. However, experience with other OCs **given in the 21-7 day's regimen will be used to** compare this extended method to cycle control, bleeding patterns and discontinuation within the study.

7.2.3 Adequacy of Overall Clinical Experience

The sponsor presented adequate efficacy and safety data that is comparable to more contemporary OCs that have been studied over the past 10 years.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no special animal or in-vitro testing done with this product.

7.2.5 Adequacy of Routine Clinical Testing

There were no special issues associated with the routine clinical testing in this NDA submission.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic and clearance parameters of levonorgestrel and ethinyl estradiol have been well described in the literature over the past 30 years.

7.2.7 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

Potential adverse events for this drug combination have been well describe in the literature and are shown in these two clinical trials. No new or unusual adverse events were seen in the **sponsor's study**

7.2.8 Assessment of Quality and Completeness of Data

Overall, the initial assessment of the quality and completeness of safety and efficacy data is considered good but not excellent. Review of CRF reveals efficacy data that is incomplete (e.g. there was no data on the number of new acceptors vs. switchers in the original data base). Efficacy data relating to pregnancies were deficit. Ultrasound reports that might have confirmed

or not confirmed dating of pregnancies were missing. Data was not submitted in a manner that would allow this reviewer a certain degree of certainty that the subject did not become pregnant while in the study. Additional data is being sought to clarify the pregnancy rate (both Pearl index and Life table analyses.) Safety data appears to be complete and sufficient

7.2.9 Additional Submissions, Including Safety Update

The safety update was presented by the sponsor on September 27, 2005. The 4-month safety update contains information that was not available at the time of filing the NDA. The following safety information was supplied:

- **Poststudy pregnancy and return to spontaneous menses follow-up information for subjects who participated in study 313-NA.**
- **Results of study 0858A2-314-NA (314-NA), an observational rollover study from study 313-NA, that captured the time to return to spontaneous menses or pregnancy in subjects with 6 to 13 pill packs of exposure to continuous-use LNG 90 µg/ EE 20 µg in study 313-NA.**
- **Preliminary information from study 0858A2-320-CA (320-CA), an ongoing 1-year extension to study 313-NA.**
- **Any serious adverse drug experiences not previously reported (if any) for this IND from the official internal database (described in section 5) through 14 Jun 2005.**

Pregnancy Information
The sponsor submitted information with complete post-study follow-up on 1,285 subjects. Thirty five (35) subjects reported that they planned to become pregnant in the 12 months following study 313-NA. Of these 35 subjects, 15 reported becoming pregnant within 3 months and 5 more within 12 months for a total of 20 subject. Of the remaining 15 subjects all reported return to spontaneous menses.

Of the 1,250 subjects who had not reported that they planned to become pregnant within 12 months, 11 subjects become pregnant within 3 months and 3 subjects became pregnant within 12 months. Therefore, a total of 36 subjects reported becoming pregnant in the post study evaluation: 27 subjects within 3 months and an additional 9 subjects within 12 months.
Return to Menses
There were 613 subjects who reported a return to menses; 535 did not report whether or not they were using hormonal contraception. This was because the post-study CRF did not require this information to be provided unless it was indicated that the subject had not returned to spontaneous menses.

Of the 672 who reported no spontaneous menses, 640 (95.2%) were using hormonal contraception. There were 29 (2.3%) of subjects out of the 1,285 responders who did not have spontaneous menses within 6 months and did not report using hormonal contraception; 14 of these subjects also reported being pregnant within 3 months on the post-study follow-up form.

Of the remaining 15 subjects, on later inquires to the clinical sites, 4 returned to spontaneous menses, 4 resumed contraceptive use, 2 became pregnant and 5 were lost to follow-up.

Study 0858A2-314-NA
This was a 3-month observational study to evaluate the time and incidence to return to spontaneous menses or pregnancy following participation for 6 to13 pill packs in the phase 3, multicenter study 313-NA.

The estimated 25th, 50th, and 75th percentiles of time (in days) to return to spontaneous menses or pregnancy in the population of subjects who completed study 314-NA were calculated with 95%CI. The 50th percentile is the median time to return to menses or pregnancy. In completed subjects the estimated time to return to menses or become pregnant was 32 (CI 31,33) days. Similar results were obtained for the 2 other populations analyzed in study 314NA: subjects who completed 313-NA and those in the ITT population.

There were no deaths or serious adverse events. Adverse events occurred in ≥5% of subjects were observed for dysmenorrhea and headache (15.2% each); all other events occurred less frequently.

Study 0858A2-320-CA
This is an ongoing phase 3 single-treatment, multicenter, open-label, 1-year extension study being conducted at 7 sites in Canada with subjects who completed study 313-NA. Of these sites, 1 site is conducting an endometrial histology extension sub-study. Completion is expected in September 2005.

As of June 25, 2005 there were 2 serious adverse events reported. One subject attempted suicide and the second subject had a panic attack.

IND Safety Reports
There were no 15-day IND safety reports for the continuous use regimen submitted to the Agency from January 1, 2005 to June 14, 2005.

Postmarketing reports
LNG 90µg/EE 20µg is not currently marketed

Reviewer's Conclusion
Since the NDA was submitted, there have been no serious or unexpected adverse events that were considered to be possibly, probably, or definitely related to the continuous-use regimen of LNG 90µg/EE 20µg.

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

This section is not applicable.

7.4 General Methodology

The sponsor has followed the general methodological blueprint used for approval of OCs developed over the past 40 plus years. Efficacy and safety data are provided entirely in electronic Common Technical Document (eCTD) format prepared according to the FDA Draft Guidance for Industry: Providing Regulatory Submissions **in Electronic Format—Human Pharmaceutical** Product Applications and Related Submissions, issued in august 2003. This submission is organized in modules 1-5.

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

Historically, efficacy data from oral contraceptive studies have ***not*** been combined. Oral contraceptive studies originally had many more cycles than presently studied. It was not unusual for some products to have 20,000 to 30,000 cycles of safety and efficacy data. More recently, in the 1980s and 1990s studies usually involved between 10,000 and 20,000 de novo subjects. Studies were reviewed separately in and effort to show consistency between studies. Safety data has always been combined in an effort to demonstrate the overall safety of a product. In this NDA, the US study 0858A2-313-NA is the primary efficacy study and is clearly powered to demonstrate safety and efficacy alone; study 0858A2-315-EU is not large enough to assess pregnancy rates; it is supportive for overall efficacy (not any worse than a marketed product) and safety is reviewed as total events. Importantly, the sponsor did not state a priori that efficacy data would be combined for the two studies.

7.4.1.1 Pooled data vs. individual study data

As stated earlier in this review efficacy data was ***not*** pooled for the 2 pivotal trials. Pill cycles were much larger in study 313-NA compared to the comparative trial 315-EU . Safety data was reviewed separately for each study to compared differences between study populations. Review of pooled safety data suggests there is no usual safety problems associated with this product and overall this product appears safe.

7.4.1.2 Combining data

Combined data was used to support the overall safety of this product.

7.4.2 Explorations for Predictive Factors

The primary factors which may have affected the overall efficacy this product are the lower (10μg) LNG and the continuous use of LNG 90μg/EE 20μg over a 1 year period. It is not known if the pregnancy rate will be at a steady monthly rate over the 13 cycles compared to most pregnancies occurring in the first 2-6 months for the standard use OC. The endometrial sub-study was performed in an effort to show stabilization of the endometrium rather than an atrophic endometrium that might predispose the subject to greater bleeding.

7.4.2.2 Explorations for time dependency for adverse findings

Cycle control and bleeding profile are very important when evaluating the overall discontinuation rates of this product. Discontinuations may be very important in subjects being placed at greater risk for pregnancy because after discontinuation of oral contraceptives subjects tend to use either ***no method of contraception or a less effective method of contraception.***

7.4.2.5 Explorations for drug-drug interactions

There are multiple drug-drug interactions that have been well-documented with OCs that have been demonstrated with different products. This if fully described in the class-label for oral contraceptive products and is consistent with use of LNG 90μg/EE 20μg.

7.4.3 Causality Determination

There were no usual or unexpected causality determinations seen in this review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor has decreased the amount of progestin in this regimen by 10mcg per day. The primary method of suppression of ovulation is in the progestin component of the OC with the estrogen component supplying some additional suppression of ovulation, but more importantly the estrogen supports cycle control. In comparing the Alesse® (LN100μg/EE 20μg) it is clear that the ***cyclic*** regimen has better control of all types of bleeding and that fewer subjects discontinue from the study. Furthermore, in comparing this product to Seasonale® (LN150μg/EE 30μg) it is apparent that the continuous dosing regimens (as seen in the Seasonale studies) leads to less cycle control (more bleeding throughout the prolonged cycles) compared to the standardized 21-28-day regimens.

8.2 Drug-Drug Interactions

There were no unknown drug-drug interactions seen in this study. Drug-drug interactions are well defined for oral contraceptives and this OC is a lower dose product compared to many marketed products.

8.3 Special Populations

There were no special populations studied with this product. Additional indications may be sought for this product that is in the same patient population that is studied for contraception.

8.4 Pediatrics

The sponsor has asked for a Pediatric waiver. This reviewer is in agreement that a waiver is appropriate.

8.5 Advisory Committee Meeting

This reviewer would not anticipate an Advisory Committee meeting should this product not be approved. This option will be offered to the company in the event of a non-approvable action, but this reviewer doubts that the company would pursue this option. However, because of the apparent drift up in the Pearl index and Life table analyses of the pregnancy rates reported with this product and others lower dose and continuous products, this reviewer feels that it is important to take the issues of acceptable Pearl index analysis of the pregnancy rate, the effect of high discontinuation rates and poor cycle control to the Reproductive Health Advisory Committee in the very near future.

8.6 Literature Review

There was no literature review associated with this product. In-house comparisons were used to address bothersome issues relating to the pregnancy rate which continues to escalate (pregnancy rate creep) higher than former divisional reviews as well as continuing higher discontinuation rates which show less cycle control and probably more unintended pregnancies.

8.7 Postmarketing Risk Management Plan

There were no new safety issues identified with this product.

8.8 Other Relevant Materials

The sponsor was asked to supply additional materials relating to the CRF. Additional source materials were sought and were supplied by the company relating to the pregnancy rate, discontinuations and follow-up of subjects who received the test article.

9 OVERALL ASSESSMENT

The continuous-use method of oral contraceptives is being developed to provide women with another option of birth control. Theoretically, it was envisioned that women on the continuous method of oral contraceptives would have no bleeding (amenorrhea) or very little bleeding or spotting over each 28-day pill cycle. Review of Lybrel and the other extended use OC Seasonale suggests that women are being exposed to a method with less cycle control and higher discontinuation rates than seen with the traditional 21-day on 7-day off OC. Lybrel™ has a higher pregnancy rate than Seasonale, a higher discontinuation rate and less cycle control than Seasonale. Most importantly, a Pearl index of 2.38 (CI 1.51, 3.37) and Life table analyses of 0.0348 (CI 0.0227,0.0539) suggests that women will be exposed to one of the least effective oral contraceptive the Division has evaluated and approved in a 13-cycle non-comparative study.

Combined with the highest discontinuation rate of 56.8% (with one-half of discontinuation associated with bleeding) and poor cycle control, this reviewer recommends non approval of this product. Safety is not considered a major concern with this product except for the fact that in demonstrating a higher rate of discontinuations and unexpected bleeding, the subject is at an increased risk for unintended pregnancy.

9.1 Conclusions

This reviewer concludes that this product does not provide an acceptable level of contraceptive effectiveness and should not be approved. Safety is not considered a major concern with this product.

9.2 Recommendation on Regulatory Action

A letter of non approval should be sent to the sponsor.

9.3 Recommendation on Postmarketing Actions

There are no recommendations regarding postmarketing action

9.3.1 Risk Management Activity

There is no additional risk management activity for the sponsor.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

The sponsor had a previously approved label for its oral contraceptive products in June 2005. With this in mind, major changes have been added to the following sections:

Changes made to the Physician's **draft label as provided by the sponsor are as follows:**

Clinical Pharmacology:
Clinical Pharmacology will be addressed by the Pharmacology team. Reviews are not finalized because of changes in the manufacturing process. In study 313NA the sponsor used a —— b(4)

method that is similar to what is being used in the manufacturing of Alesse®. In study 315EU a [redacted] method was used that improves available drug by about 4% compared to the [redacted] method. At present, there are no bridging studies between these products.

b(4)

Pharmacokinetics:
Final review is not available at this time. Again there are issues with the PK of the marketed product and the to-be-marketed product. There may be a [redacted] difference in release of drug between the [redacted] method vs. the [redacted] method.

[redacted]

b(4)

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_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

b(4)

9.5 Comments to Applicant

There are no direct comments from this reviewer. Comments will be made regarding the approvability of this product at a higher level than the reviewing medical officer.

10 APPENDICES

10.1 Study 0858A2-315-EU

The primary objective of this study was to evaluate the safety and contraceptive efficacy of a continuous-use regimen of LNG 90µg/EE 20µg compared with a cyclic regimen of LNG 100µg/EE 20µg for 21 days followed by 7 pill free days. The secondary objective of this study is to evaluate the effects of the continuous and cyclic regimens on vaginal bleeding profile, carbohydrate, lipid, hemostatic balance, and bone metabolism measures, sex hormone binding globulin (SHBG) and hemoglobin levels, discontinuation rates, compliance with respect to pill taking and subject satisfaction.

Overall Study Design and Plan Description

Study 315-EU was initiated in March 2003 and was completed in October 2004. This is a Phase 3, randomized, multicenter, open-labeled study that was to be conducted at approximately 44 sites in Europe. At approximately 6 sites there were 24 subjects who were to participate in a metabolic sub-study. A total of 600 subjects were to be enrolled in the basic study. Of these, approximately 300 subjects were to be randomly assigned to take LNG 90µg/EE 20µg continuous for 1 year, and approximately 300 subjects were to randomly assigned to take LNG 100µg/EE 20µg cyclically for 21 days followed by 7-pill-free days for 1 year. Approximately 144 subjects (72 per treatment group) were to participate in the metabolic sub-study.

Basic Study Flowchart

This is very similar to flowchart Table 2 (Sponsor Table 6.1-1

Study Conduct

Study conduct was very similar to study 313-NA.

Study Design, Including Choice of Control Groups

This was a randomized open-labeled study. This study compared the safety and contraceptive efficacy of LNG 90µg/EE 20µg in a continuous-use regimen with a cyclic regimen of LNG 100µg/EE 20µg for 21 days followed by a pill free interval of 7 days. The comparator is marketed under several trade names, including Loette® in the EU and Alesse® in the US.

Inclusion and Exclusion Criteria

Identical to study 0858A2-313-NA

Identity of Investigational Product

Table 27 Product Information

Investigational Product	Formulation	Batch Number	Site of Manufacture
LNG 90 µg/EE 20 µg tablets	0931760C	A22646	Guayama, Puerto Rico
	0931921C	A59604	Guayama, Puerto Rico
LNG 100 µg/EE 20 µg tablets	0931845C	A16503	Newbridge, Ireland
	0931845C	A16504	Newbridge, Ireland
	0931845C	A47337	Newbridge, Ireland

Method of Assigning Subjects to Treatment Groups

This was an open-label study. Subjects were randomly assigned to receive either LNG 90µg/EE 20µg continuously for 1 year or LNG 100µg/EE 20µg for 21 days followed by a 7-day, pill-free interval for 1 year. Forty-four sites participated in this study; 40 sites in the basic study and the other 4 sites in both the basic study and the metabolic study.

Permitted Therapy/Prohibited Therapy

Identical to study 0858A2-313-NA

Efficacy and Safety Variables

Identical to study 0858A2-313-NA

Statistical Methods Planned in the Protocol and Determination of the Sample Size

The statistical methods were identical to study 0858A2-313-NA except for the determination of sample size for this comparative study.

Determination of Sample Size

Approximately 600 subjects (300 in each treatment group) were to be enrolled in this study, and approximately 144 of the 600 were to participate in a metabolic sub-study. For the metabolic sub-study, approximately 144 subjects (72 per group) were to be enrolled, 50 subjects per group were expected to complete the study. Assuming a standard deviation of 0.7, 50 subjects per group would provide 90% power to detect a difference of 0.458 mmol/L in total cholesterol values between treatment groups, using a 2-sided test at the 5% level of significance.

Changes in the Conduct of the Study or Planned Analyses
Because many termination study visits occurred during the summer vacation season in 2004, some final visits were performed 1 cycle earlier or later, depending on subject and investigator availability. Thus, some subjects were allowed to continue taking study drug after cycle 13; no subjects took more than 2 additional pill packs. In this report, efficacy data for these subjects are presented only through pill pack 13.

Subject Satisfaction

Frequency distributions and summary statistics for the responses to the subject satisfaction questionnaire was provided by visit. A comparison of the distribution of the 5 possible responses were done between treatment groups at each time point using the Fisher exact test. Subjects were asked the following question at visit 1A: **"In the past 6 months, have you used any of these birth control products?" The options** were oral contraceptive, transdermal patch, **and vaginal ring. Subjects who responded "Yes" were asked the following question: "Please** rate how satisfied you were with the most recent birth control product that you have been **taking." At each subsequent visit, the following** question was asked of each subject, regardless **of prior use: "Please rate how satisfied you were** with the birth control pill that you have been **taking in this study." Responses to the subject sa**tisfaction questionnaire were analyzed by visit.

Metabolic Sub-study
The effects on laboratory indexes of carbohydrate, lipid, hemostasis, and bone metabolism measures, and SHBG levels were compared between subjects who received the continuous-use regimen of LNG 90µg/EE 20µg and those who received the cyclic regimen of LNG 100µg/EE 20 µg (21 days followed by a 7-day, pill-free interval).

Study Subjects

Disposition of Subjects

One thousand- one hundred and sixteen (1,116) subjects were screened. Four-hundred sixty-five (465) subjects were screen failures and 10 subjects had no data after the baseline evaluation. Of the 641 subjects who received at least 1 dose of study drug, 323 were randomly assigned to take

LNG 90µg/EE 20 µg continuously for 1 year, and 318 subjects were randomly assigned to take LNG 100µg/EE 20 µg for 21 days followed by 7 pill-free days for 1 year. A total of 147 subjects (74 continuous-use, 73 cyclic-use) participated in the metabolic sub-study. The disposition of all subjects in the study is shown in the following **Figure 2 (Sponsor's Figure 8.1-1)**

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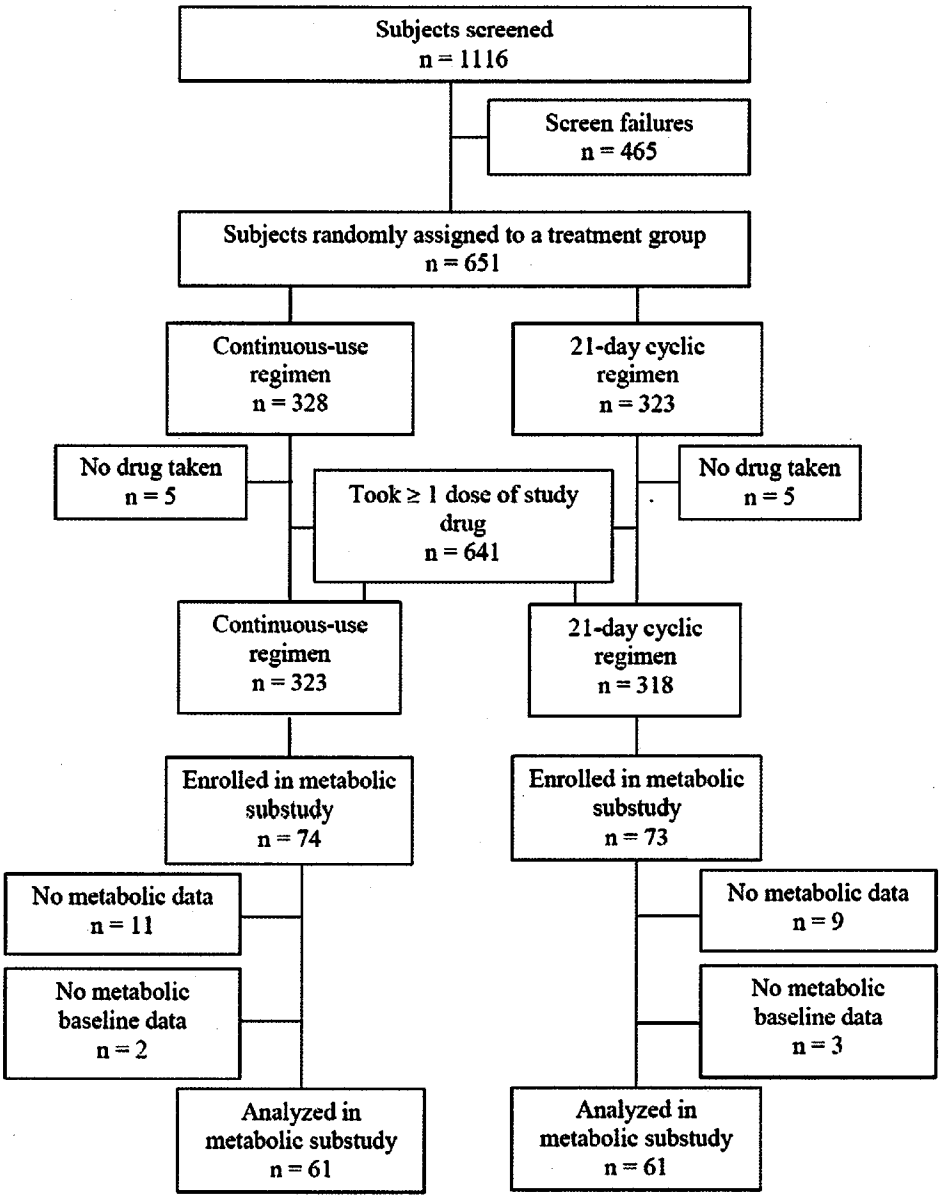
Figure 2 Appendix Disposition of Subjects

Figure 8.1-1: Subject Disposition



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Discontinuations

Overall, 176 (27%) of subjects discontinued from the study: 107 subjects in the continuous use treatment group and 69 (22%) in the 21-day cyclic regimen (p<0.001). The primary reasons for discontinuations are summarized in the following table.

Table 28 Number (%) of Subjects who Discontinued from the Study by Primary Reason, Safety Population Sponsor's Table 8.1.1-1

Reason	LNG 90 µg/EE 20 µg n = 323	LNG 100 µg/EE 20 µg n = 318	Overall p-Value[a]
Total[b]	107 (33.1)	69 (21.7)	0.001**
Accidental pregnancy[c]	0 (0.0)	3 (0.9)	0.122
Adverse event	72 (22.3)	31 (9.7)	<0.001***
Investigator request	1 (0.3)	2 (0.6)	0.621
Lost to follow-up	5 (1.5)	2 (0.6)	0.451
Planning pregnancy	3 (0.9)	3 (0.9)	1.000
Protocol violation	9 (2.8)	11 (3.5)	0.656
Subject request	17 (5.3)	17 (5.3)	1.000

a: p-Value obtained from the Fisher exact test (2-tail).
b: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
c: One (1) accidental pregnancy in the LNG 90 mg/EE 20 mg group occurred with an EDC 6 days after the last dose of study drug and therefore, did not discontinue early from the study.
* Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

Note: The difference between treatment groups in the total discontinuations rate are attributable to a difference in withdrawals because of adverse events (p <0.001). Note that the discontinuation rate is markedly lower 107 (33.1%) compared to the US trial where 1,213 (56.8%) of subjects discontinued. Also note that the 21.7% discontinuation percent is significantly lower than the continuous treatment group (33.1%). Note than 34 (5.3%) of subjects discontinued due to subject request compared to 336(15.7) in the US trial and that 5 (1.5%) were lost to follow-up compared to 223 (10.4%) in the US trial.

Note adverse events are the primary reason for discontinuation of study drug with subject request as the second reason for discontinuation. Sponsor's table 10.3.1.3-1 reported the number of subjects reporting adverse in more detail. Under body system any adverse event, 72 (22.3%) subjects in the LNG 90µg/EE 20µg group discontinued from the study compared to 31 (9.7%) subjects in the LNG 100µg/EE 20µg group. All other body systems are very similar in adverse events ***except*** the urogenital system were bleeding was a substantial problem as seen in the US study. See modified sponsor's table 10.3.1.3-1 which focuses on the urogenital system:

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Table 29 Modified Table 10.3.1.3-1 Number **(%) of Subject's Reporting Adverse Events as** Primary Reason for Discontinuation of Study Drug

Body System Adverse Event	LNG 90 µg/EE 20 µg n = 323	LNG 100 µg/EE 20 µg n = 318	Overall p-Value[a]
Urogenital			
Breast pain	2 (0.6)	1 (0.3)	1.000
Cervix carcinoma in situ	1 (0.3)	0 (0.0)	1.000
Cervix disorder	2 (0.6)	0 (0.0)	0.499
Dysmenorrhea	1 (0.3)	1 (0.3)	1.000
Mastitis	1 (0.3)	0 (0.0)	1.000
Menorrhagia	4 (1.2)	1 (0.3)	0.373
Metrorrhagia	28 (8.7)	9 (2.8)	0.002*
Uterine hemorrhage	3 (0.9)	0 (0.0)	0.249
Vaginal hemorrhage	12 (3.7)	2 (0.6)	0.012*

*Denotes statistical significance at the 0.05, 0.01, or 0.001 levels.
a: Fisher exact test (2-tail) was used to determine overall p-values.

Note bleeding disorders menorrhagia, metrorrhagia, uterine hemorrhage and vaginal hemorrhage. Forty- seven (47) of 72 (65.2%) in the LNG 90µg/EE 20µg group reported adverse events relating to these 4 bleeding disorders compared to12 of 31 (38.7%) for the LNG 100µg/EE 20µg group. This is highly significant and even though subjects may not have bleed to an extent that they become anemic, it is clear that bleeding disorders significantly impact upon women lives and they will seek other alternatives.

Demographic and Other Baseline Characteristics

The demographic and other baseline characteristics are reported in Table 8.2.1-1. This table will not be reproduced, but will be summarized in the following paragraphs.

This table reports that for the total study population of 641 subjects, 618 (96.4%) were white, 9 (1.4%) were black, 5 (0.8%) were Asian and 9 (1.4%) were described as other. The mean age was 27.35 years, the mean height was 167.48 cm, the mean weight was 63.86kg and the body mass index was 22.74 kg/m^2.

Additionally, 392 (61.1%) of subjects had no pregnancies, 105(16.3%) were nulliparous, 99 (15.4%) had been pregnant twice, 37 (5.7%) had been pregnant three times, 14 (2.1%) had been pregnant 4 times, 2 (<1%) had been pregnant 5 times, and an additional 8 (1.2%) subjects had been pregnant from 6-10 times. There were 452 (70.5%) subjects who were non-smokers, and 189 (29.5%) who were smokers. In the smoking group subjects smoked on average 8.04 cigarettes per day. Subjects on average had 13.82 years of education.

There were 544 subjects in the study total population aged 35 years or younger at the time of enrollment. These subjects had demographic and baseline characteristics (i.e. race, height, weight, BMI, and previous pregnancies) similar to those in the total population, but were younger with a mean age of 25.18 years; there were more nulliparous subjects in the <35 age group were (67.5% vs. 61.1%), otherwise the groups were very similar.

Reviewer's Comment
Baseline characteristics are dissimilar primarily in two areas. Compared to the US population, there was markedly fewer blacks and in this study and no Hispanics. Also, as has been seen in most studies, the US population has a greater BMI(14-15lbs) than in the European study. This suggest the two subject populations are dissimilar

Metabolic Sub-study

There were 147 subjects enrolled in this study. A total of 109 (74.1%) completed the sub-study.

Concomitant Therapy

8.3 Concomitant Therapy
Concomitant therapy was received by 256 (79%) subjects with the continuous-use regimen and 263 (83%) subjects with the 21-day cyclic regimen during the study. The most frequently used classes of concomitant medications in the continuous-use regimen and cyclic regimen were analgesics and antipyretics (45.8% and 48.7%, respectively); anti-inflammatory/antirheumatic products, nonsteroidals (38.4% and 45.3%, respectively); and antihistamines for systemic use (11.8% and 12.6%, respectively).

A total of 7 subjects, 1 treated with the continuous-use regimen and 6 subjects treated with the cyclic regimen had pill packs excluded from the evaluation of contraceptive efficacy because of non-study concomitant medications that might have affected the outcome of the study. One subject (315-042-1902) in the LNG 90µg/EE 20µg group use the antibiotic clarithromycin; 5 subjects (315-008-0228, 315-011-0499, 315-018-0767, 315-022-0979, 315-044-1957) used prohibited antibiotics and the sixth subject 315-026-1158 used an antipsychotic/antiepileptic drug.

Efficacy Evaluation

Total Population

Of subjects who took study drug, some of the data for 323 subjects who received continuous use LNG 90µg/EE 20µg and 318 subjects who received cyclic LNG 100µg/EE 20µg were excluded from the efficacy analyses because of failure to meet 1 or more of the criteria for evaluability. A total of 3,072 (89%) pill packs in the continuous-use regimen and 3,270 (88%) pill packs in the cyclic regimen were included in the Pearl index analyses. The number of pill packs excluded from Pearl index analyses is summarized by treatment group and reason for exclusion in the following table:

Table 30 Number (%) of Pill Packs Excluded From the Pearl Index by Reason Sponsor's Table 9.1.1-1

	LNG 90 µg/EE 20 µg (n = 3461)	LNG 100 µg/EE 20 µg (n = 3698)
Total pill packs included	3072 (89)	3270 (88)
Total pill packs excluded[a]	389 (11)	428 (12)
Backup contraception used	134 (4)	225 (6)
Missed ≥ 3 consecutive pills	21 (< 1)	21 (< 1)
Missed ≥ 5 pills total in any pill pack	18 (< 1)	16 (< 1)
Prohibited medication	2 (< 1)	22 (< 1)
Not sexually active or unknown	237 (7)	176 (5)

a: A pill pack may have been excluded for more than 1 reason. Only the pill packs to which these criteria apply were excluded.

Note that the number of excluded cycles is very similar 11% vs. 12%. Also note that a greater number of subjects used backup contraception in the LNG 100µg/EE 20µg group while more subject were not sexually active in the LNG 90µg/EE20 µg.

Excluded from Pearl index analyses for 1 or more of the reasons listed were 389 (11%) continuous-use regimen pill packs and 428 (12%) cyclic regimen pill packs.

Table 31 Pill Packs Valid for Analysis, Total Population Sponsor's Table 9.1.1-2

	---------- Number of Pill Packs ----------	
Type of Evaluation	LNG 90 µg/EE 20 µg n = 3461	LNG 90 µg/EE 20 µg n = 3698
Pearl Index	3072	3270
Life table analysis	2360	2627

A total of 2,360 (68%) pill packs in the continuous-use regimen and 2,627 (71%) pill packs in the cyclic regimen were included in the Life table analysis. The number of pill packs excluded from the life table analysis is summarized in the following table:

Table 32 Number (%) of Pill Packs Excluded From the Life Table Analyses By Reason, Total Population Sponsor's Table 9.1.1-3

	LNG 90 µg/EE 20 µg (n = 3461)	LNG 100 µg/EE 20 µg (n = 3698)
Total pill packs included	2360 (68)	2627 (71)
Total pill packs excluded[a]	1101 (32)	1071 (29)
Backup contraception used	440 (13)	613 (17)
Missed ≥ 3 consecutive pills	77 (2)	52 (1)
Missed ≥ 5 pills total in any pill pack	69 (2)	35 (< 1)
Prohibited medication	0 (0)	49 (1)
Not sexually active or unknown	588 (17)	387 (10)

a: A pill pack may have been excluded for more than 1 reason. The pill packs to which these criteria apply and any subsequent pill packs were excluded.

Note than almost one-third of cycles were excluded from the Life Table analyses for both groups, 1,101 (32%) in the continuous group and 1,071 (29%) in the cyclic regimen pills. Note excluded cycles in both groups for backup contraception or **"not sexually active or unknown."** are almost identical when combined.

Subjects Who Were Aged 35 Years or Younger at Study Start

A total of 2,564 (89%) pill packs in the continuous-use regimen and 2,733 (88%) pill packs in the cyclic regimen were included in the Pearl index analyses for 544 subjects who were aged 35 years or younger at the beginning of this study. The number of pill packs excluded from the Pearl index analyses is summarized by treatment group and reason for exclusion in the following table:

Table 33 Number (%) of Pill Packs Excluded From the Pearl Index by Reason for Subjects Aged 35 Years or Younger at Study Start Sponsor's Table 9.1.2-1

	LNG 90 µg/EE 20 µg (n = 2881)	LNG 100 µg/EE 20 µg (n = 3116)
Total pill packs included	2564 (89)	2733 (88)
Total pill packs excluded[a]	317 (11)	383 (12)
Backup contraception used	107 (4)	204 (7)
Missed ≥ 3 consecutive pills	16 (< 1)	21 (< 1)
Missed ≥ 5 pills total in any pill pack	16 (< 1)	16 (< 1)
Prohibited medication	2 (< 1)	15 (< 1)
Not sexually active or unknown	195 (7)	158 (5)

a: A pill pack may have been excluded for more than 1 reason. Only the pill packs to which these criteria apply were excluded.

Note the number of subjects in 35 years or younger group is greater than the total population. Also note less use of backup contraception compared to the total population; in addition, note a **much smaller number of subjects who were "not sexually active or unknown" in the aged 35** years or younger group compared to the total population.

The following table shows the number of pill packs valid for the Life table analysis and the calculation of the Pearl index by treatment group.

Table 34 Pill Packs Valid for Analysis, Subjects Aged 35 Years or Younger at Study Start

	Number of Pill Packs	
Type of Evaluation	LNG 90 µg/EE 20 µg n = 2881	LNG 100 µg/EE 20 µg n = 3116
Pearl Index	2564	2733
Life table analysis	1977	2180

Note in both analyses that there are approximately 600 less cycles for calculation of the Life table analyses *compared* to the Pearl's index for both treatment groups. This is consistent with the US study where a significant number of subjects could not be utilized in the Life table analyses because of discontinuations. Overall, a total of 1,977 (69%) pill packs in the continuous –use regimen and 2,180 (70%) pill packs in the cyclic regimen were included in the Life table analyses for subjects 35 years or younger at study start.

Table 35 Number (%) of Pill Packs Excluded From the Life Table Analyses by Reason, Subjects Aged 35 or Younger at Study Start Sponsor's Table 9.1.2-3

	LNG 90 µg/EE 20 µg (n = 2881)	LNG 100 µg/EE 20 µg (n = 3116)
Total pill packs included	1977 (69)	2180 (70)
Total pill packs excluded[a]	904 (31)	936 (30)
Backup contraception used	384 (13)	547 (18)
Missed ≥ 3 consecutive pills	66 (2)	52 (2)
Missed ≥ 5 pills total in any pill pack	66 (2)	35 (1)
Prohibited medication	0 (0)	36 (1)
Not sexually active or unknown	458 (16)	331 (11)

a: A pill pack may have been excluded for more than 1 reason. The pill packs to which these criteria apply and any subsequent pill packs were excluded.

Note 31% of subjects were excluded in the continuous group compared to 30 % who were excluded in the cyclic regimen pill packs. Also note there was a greater percentage of subjects in the cyclic group who were excluded for use of backup contraception, while a greater percentage of not sexually active or unknown subjects were excluded in the continuous use group.

Treatment Compliance

The percentage of pill packs with any pills missed was significantly higher ($p < 0.001$) in the continuous group (14%) compared to the cyclic group (8%).

Pregnancy rates

The following table summarizes 4 pregnancies that occurred in study 315-EU

Table 36 Summary of Pregnancies Classified as Method Failure or User Failure Sponsor's Table 9.4.2.1-1

Subject Number	Classification	Total Duration on Study Medication	Estimated Date of Conception (Relative Day)
	LNG 90 µg/EE 20 µg Continuous		
315-001-0013	Not classified[a]	364	Posttreatment (6 days)
	LNG 100 µg/EE 20 µg Cyclic		
315-026-1147	Method failure	245	211
315-034-2252	User failure	189	179
315-034-2247	User failure	294	289

a: Not classified for the Pearl Index. Subject was compliant with respect to taking study drug within 30 days of EDC (including the posttreatment portion of that 30 day period, when study drug was not taken), and was classified as a method failure for the life table.

The following is a short synopsis of the pregnancies that occurred in study 315-EU:

- **315-001-0013 is classified by sponsor as "*not classified*" post-treatment day 6. This** subject was in the trial for 367 days. She had a site visit [redacted] and a negative urine pregnancy test. She started pill pack 13 on July 26, 2004 and is presumed to have continued her OC. On [redacted] she had a positive urine pregnancy test and an early ultrasound on [redacted]. No ultrasound dating of the pregnancy is reported. ***This reviewer assesses this pregnancy as on-treatment unless the early ultrasound on*** [redacted] ***reports otherwise.*** b(6)
- Subject 315-034-2247 was classified by the sponsor as a ***user*** failure after 294 days in the trial. This subject was taking Loette (LN 100µg/EE 20µg) in a cyclic manner. The subject had a negative urine pregnancy test on [redacted] and a positive urine test on [redacted]. The subject was compliant with the test article until June 6, 2004 when ***she missed 1 tablet during week 1 of pill pack 11. She took 2 tablets the next day***. The ***investigator*** considered the pregnancy ***not related*** to test article while the medical monitor listed it as a user failure. b(6)
- Subject 315-034-2252 was classified by the sponsor as a ***user*** failure. The subject was in the trial for 206 days. This subject was taking Loette (LN 100µg/EE 20µg) in a cyclic manner On [redacted] the subject had a positive urine pregnancy test and on [redacted] the she had a positive serum pregnancy test. Conception was determined by the **subject's history although the investigator** reported the subject started ***vomiting 1-2.5 hours after pill intake*** on [redacted]. Tablets taken by the subject on days 174-175 are not consistent with the CRF. There is no ultrasound data given; a birth date of [redacted] is recorded. b(6)
- Subject 315-026-1147 was classified as a ***method*** failure. This subject was taking Loette (LN 100µg/EE 20µg) in a cyclic manner. The subject had a positive urine pregnancy test at home on [redacted] ***She was compliant with the test article***. She was seen at a clinic visit on [redacted] post-treatment) for a visit and had a positive urine pregnancy test. The estimated date of conception was [redacted] (tabulation not b(6)

clear). Of interest the ***investigator*** considered the pregnancy probably ***not related to test article*** while the medical monitor listed it as a method failure.

In the total population ***(including days 1 to14)*** the Pearl index and 95% confidence interval for the LNG 90 µg/EE 20 µg continuous pill packs is **0.42** (0.01, 2.36). The total number of pill packs was 3,072. The Pearl index and 95% confidence interval for the LNG 100 µg/EE 20 µg cyclic pill packs is **1.19** (0.25,3.48).

In the total population of 35 years or younger age ***(including days 1 to 14)*** the Pearl index and confidence interval for the LNG 90 µg/EE 20 µg continuous pill packs is **0.51** (0.01, 2.82). The total number of pill packs was 2,564. The Pearl index and 95% confidence interval for the LNG 100 µg/EE 20 µg cyclic pill packs is **1.43** (0.29,4.17). The total number of pill packs was 2,733.

The Life table analysis(total population) of withdrawals due to accidental pregnancies reports a cumulative termination rate for accidental pregnancy of LNG 90 µg/EE 20 µg continuous use regimen at pill pack 13 was **0.0095**. The 13 pill pack cumulative termination rate for the LNG 90 µg/EE 20 µg continuous- use regimen per woman was **0.2954**.

The Life table analysis (total population) of withdrawals due to accidental pregnancies reports a cumulative termination rate for accidental pregnancy of LNG 100 µg/EE 20 µg cyclic at pill pack 13 was **0.0148**. The 13 pill pack cumulative termination rate for the LNG 100 µg/EE 20 µg cyclic use regimen per woman was **0.1827**.

The Life table analysis subjects aged 35 years or younger of withdrawals due to accidental pregnancies reports a cumulative termination rate for accidental pregnancy of LNG 90 µg/EE 20 µg continuous use regimen at pill pack 13 was **0.0110**. The 13 pill pack cumulative termination rate for the LNG 90 µg/EE 20 µg continuous- use regimen per woman was **0.3347**.

The Life table analysis subjects age 35 years or younger of withdrawals due to accidental pregnancies reports a cumulative termination rate for accidental pregnancy of LNG 100 µg/EE 20 µg cyclic at pill pack 13 was **0.0180**. The 13 pill pack cumulative termination rate for the LNG 100 µg/EE 20 µg cyclic use regimen per woman was **0.2002**.

Reviewer's Comments

Approximately 30%-31% of cycles were excluded from the efficacy analyses. The Pearl index in the age group 35 or younger in the continuous LNG 90 µg/EE 20 µg regimen is 0.51. This is clearly lower than what was seen in the US trial. The only pregnancy that was diagnosed in the LNG 90 µg/EE 20 µg continuous group occurred 6 days post-treatment (according to the sponsor). This reviewer is not in agreement with this assessment and has documented this as an in-treatment pregnancy (method failure). It is interesting to note that the 3 pregnancies occurred after 6 months of treatment in the cyclic regimen occurred from 179 days to 289 days. Pregnancies in this trial are clearly different in occurrence from the US trial where pregnancies were reported pre-therapy, during treatment and post-therapy. Reasons for differences in pregnancies are not clear to this reviewer but the total number of cycles is much lower than study 315US and better patient compliance and a

different subject population appears to comprise much of the differences seen between the two studies. Also, the women in the US trial are heavier by a mean of 6.5kg (14-15lbs). In conclusion, while the sample size of this small comparative study is *not large enough to assess pregnancy rates*, from an efficacy standpoint, it would appear that women who take Milibrel are not at a greater risk of pregnancy than Alesse.

The initial reason given for the continuous use oral contraceptive was that without a 7-day withdrawal period a subject could have sustained amenorrhea and sustained anovulation so that bleeding could or would not enter into her daily activities. Additionally, by not having menses on a monthly basis the symptoms relating to withdrawn of hormones, such as cycle related symptoms, could be lessen in an effort to improve a woman's quality of life. In study 315EU the incidence of amenorrhea and bleeding are compared for a cyclic vs. continuous regimen:

The following table reports the bleeding pattern by pill pack with the number and percentage of subjects with 28 days of data: Note these are large tables and the report data from the continuous regimen is followed by the cyclic regimen and will have to be shown over the next 2 pages:

Table 37 Summary of Bleeding Patterns by Pill Pack Number and Percentage of Subjects, Pill Packs with 28 days of Data Sponsor's Table 9.4.2.2.1-1

			Total				
Pill Pack	n	Amenorrhea	Bleeding (With No Spotting)	Spotting (With No Bleeding)	Bleeding and/or Spotting	Bleeding (With or Without Spotting)	No Bleeding (With or Without Spotting)
LNG 90 µg/EE 20 µg Continuous							
1	317	14 (4.4%)	43 (13.6%)	14 (4.4%)	303 (95.6%)	289 (91.2%)	28 (8.8%)
2	307	100 (32.6%)	17 (5.5%)	70 (22.8%)	207 (67.4%)	137 (44.6%)	170 (55.4%)
3	292	79 (27.1%)	16 (5.5%)	68 (23.3%)	213 (72.9%)	145 (49.7%)	147 (50.3%)
4	281	87 (31.0%)	13 (4.6%)	80 (28.5%)	194 (69.0%)	114 (40.6%)	167 (59.4%)
5	271	103 (38.0%)	9 (3.3%)	70 (25.8%)	168 (62.0%)	98 (36.2%)	173 (63.8%)
6	264	97 (36.7%)	11 (4.2%)	71 (26.9%)	167 (63.3%)	96 (36.4%)	168 (63.6%)
7	240	95 (39.6%)	7 (2.9%)	70 (29.2%)	145 (60.4%)	75 (31.3%)	165 (68.8%)
8	236	117 (49.6%)	4 (1.7%)	57 (24.2%)	119 (50.4%)	62 (26.3%)	174 (73.7%)
9	228	119 (52.2%)	2 (0.9%)	54 (23.7%)	109 (47.8%)	55 (24.1%)	173 (75.9%)
10	226	118 (52.2%)	5 (2.2%)	51 (22.6%)	108 (47.8%)	57 (25.2%)	169 (74.8%)
11	222	115 (51.8%)	5 (2.3%)	55 (24.8%)	107 (48.2%)	52 (23.4%)	170 (76.6%)
12	220	124 (56.4%)	3 (1.4%)	54 (24.5%)	96 (43.6%)	42 (19.1%)	178 (80.9%)
13	210	111 (52.9%)	4 (1.9%)	55 (26.2%)	99 (47.1%)	44 (21.0%)	166 (79.0%)

Note at cycle 6 that 97 (36.7%) of subjects are amenorrheic; at cycle 13 111(52.9%) of subjects are amenorrheic. Also review the number of subjects with various types of bleeding or spotting.

			Total				
Pill Pack	n	Amenorrhea	Bleeding (With No Spotting)	Spotting (With No Bleeding)	Bleeding and/or Spotting	Bleeding (With or Without Spotting)	No Bleeding (With or Without Spotting)
LNG 100 µg/EE 20 µg Cyclic							
1	308	0 (0.0%)	45 (14.6%)	4 (1.3%)	308 (100.0%)	304 (98.7%)	4 (1.3%)
2	296	3 (1.0%)	69 (23.3%)	8 (2.7%)	293 (99.0%)	285 (96.3%)	11 (3.7%)
3	290	2 (0.7%)	54 (18.6%)	11 (3.8%)	288 (99.3%)	277 (95.5%)	13 (4.5%)
4	292	4 (1.4%)	56 (19.2%)	16 (5.5%)	288 (98.6%)	272 (93.2%)	20 (6.8%)
5	284	1 (0.4%)	47 (16.5%)	15 (5.3%)	283 (99.6%)	268 (94.4%)	16 (5.6%)
6	281	2 (0.7%)	58 (20.6%)	6 (2.1%)	279 (99.3%)	273 (97.2%)	8 (2.8%)
7	267	6 (2.2%)	54 (20.2%)	10 (3.7%)	261 (97.8%)	251 (94.0%)	16 (6.0%)
8	266	3 (1.1%)	53 (19.9%)	17 (6.4%)	263 (98.9%)	246 (92.5%)	20 (7.5%)
9	262	5 (1.9%)	49 (18.7%)	17 (6.5%)	257 (98.1%)	240 (91.6%)	22 (8.4%)
10	254	1 (0.4%)	45 (17.7%)	8 (3.1%)	253 (99.6%)	245 (96.5%)	9 (3.5%)
11	255	4 (1.6%)	46 (18.0%)	6 (2.4%)	251 (98.4%)	245 (96.1%)	10 (3.9%)
12	255	5 (2.0%)	42 (16.5%)	10 (3.9%)	250 (98.0%)	240 (94.1%)	15 (5.9%)
13	229	3 (1.3%)	44 (19.2%)	23 (10.0%)	226 (98.7%)	203 (88.6%)	26 (11.4%)

Data for the 12 subjects with bleeding data at pill packs 14 and 15 are not shown.

Note in the cyclic method that less than 2.2% of subject achieved amenorrhea. However, amenorrhea is not the purpose of the cyclic regimen. The purpose of the cyclic regimen is consistent monthly withdrawal bleeding in over 90% cycles while no bleeding (with or without spotting is reported in 1.3% to 11.4% of subjects are cycle 13. For a true comparison one would have to look at amenorrhea during the active phase only for the cyclic regimen.

The following table reports the percentage of subjects with cumulative amenorrhea at each pill pack and subjects with complete bleeding data through pill pack 13 (continuous regimen):

Table 38 Percentage of Subjects With Cumulative Amenorrhea At Each Pill Pack: Subjects With Complete Bleeding Data Through Pill Pack 13 Sponsor's Table 9.4.2.2.2-1

Pill Packs	n (%)	(95% CI)
LNG 90 µg/EE 20 µg Continuous, N = 196		
Pill Pack 1 - 13	0 (0.0%)	(0.0, 1.9)
Pill Pack 2 - 13	8 (4.1%)	(1.8, 7.9)
Pill Pack 3 - 13	12 (6.1%)	(3.2, 10.5)
Pill Pack 4 - 13	17 (8.7%)	(5.1, 13.5)
Pill Pack 5 - 13	23 (11.7%)	(7.6, 17.1)
Pill Pack 6 - 13	32 (16.3%)	(11.4, 22.3)
Pill Pack 7 - 13	38 (19.4%)	(14.1, 25.6)
Pill Pack 8 - 13	46 (23.5%)	(17.7, 30.0)
Pill Pack 9 - 13	50 (25.5%)	(19.6, 32.2)
Pill Pack 10 - 13	58 (29.6%)	(23.3, 36.5)
Pill Pack 11 - 13	73 (37.2%)	(30.5, 44.4)
Pill Pack 12 - 13	85 (43.4%)	(36.3, 50.6)
Pill Pack 13 - 13	104 (53.1%)	(45.8, 60.2)

Note at cycle 6, 32 (16.3%) of subjects are amenorrheic; at cycle 13 104 (53.1%) of subjects are amenorrheic. These numbers and percentages are similar to the US study population where 505 (58.7%) achieved amenorrhea at cycle 13.

In conclusion, the number of adverse events leading to discontinuation is significantly different for the continuous (22.3%) vs. (cyclic 9.7%) regimens. This difference is driven by

greater bleeding events in the continuous group compared to the cyclic group. As seen in the 313-NA bleeding continues to be a significant problem with the continuous regimen.

10.2 Review of Individual Study Reports

There is no need to perform additional review of individual study reports.

10.3 Line-by-Line Labeling Review

Changes made to the Physician's draft label as provided by the sponsor are as follows:

Clinical Pharmacology:
Clinical Pharmacology will be addressed by the Pharmacology team. Reviews are not finalized as yet do to change in the manufacturing process. In study 313NA the sponsor used — — method that is similar to what is being used in the manufacturing of Alesse. In study 315EU a — — method was used that improves available drug by about 4% compared to the — — method. This may have improved efficacy in Study 315EU but there has been no bridging between these products. b(4)

Pharmacokinetics:
Final review is not available at this time. Again there are issues with the PK of the marketed product and the to-be-marketed product. There may be as much as — difference in release between the — — method vs. the — — method.

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

[redacted] b(4)

REFERENCES

1 Hatcher R, Trussell J, Stewart F, Nelson, A Cates W, Contraceptive Technology, 18th Ed. 2004.
2.Trussell J, Vaughan B, Family Planning Perspectives 1999, 31 920:64-72&93.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Phill H. Price
4/5/2006 01:31:30 PM
MEDICAL OFFICER

Shelley Slaughter
4/5/2006 01:54:18 PM
MEDICAL OFFICER
I concur.

NDA: 21-864

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	√		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	√		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	√		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	√		Study 208 was a well designed dose finding study that addressed ovulation suppression
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	√		Study 313AUS and 315EU are two well controlled studies
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	√		The above 2 studies were designed to support this NDA
7) Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	√		[redacted]
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√		

b(4)

ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	√		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	√		The two pivotal studies were designed to support US and EU registration
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-puts) previously requested by the Division	√		Additional data may be required regarding pregnancies and drop-outs in this review
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	√		
13) Has the applicant presented safety assessment based on all current world-wide knowledge regarding this product?	√		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	√		
15) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	√		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	√		

ITEM	YES	NO	COMMENT
17) Reasons for refusal to file:			

Phill H. Price, M.D. 7/12/05_____
Reviewing Medical Officer/Date

_____
Supervisory Medical Officer/Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Phill H. Price
7/12/05 11:15:07 AM
MEDICAL OFFICER

Scott Monroe
7/12/05 11:37:49 AM
MEDICAL OFFICER
I concur with Dr. Price's recommendation.