CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 27, 2013
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204-061
Applicant	Teva Branded Pharmaceutical Products, R&D, Inc.
Date of Submission	May 31, 2012
PDUFA Goal Date	March 31, 2013
Proprietary Name / Established (USAN) names	Quartette Ethinyl estradiol (EE)/Levonorgestrel (LNG) and EE alone
Dosage forms / Strength	Oral tablet; EE 20-30 µg/LNG 150 µg and EE 10 µg
Dose Regimen	91-day phasic regimen of EE/LNG for 84 days, followed by 7 days of EE alone
Proposed Indication(s)	Prevention of pregnancy
Recommended:	***Approval***

1. Introduction

This NDA seeks approval for an extended dose regimen combination oral contraceptive (COC) containing levonorgestrel (LNG) and ethinyl estradiol (EE), with EE doses that vary in a phasic manner, and that includes a 7-day EE-alone interval at the end of the combination hormone interval. The dose regimen is as follows:

Days 1-42: 20 µg EE/150 µg LNG
Days 43-63: 25 µg EE/150 µg LNG
Days 64-84: 30 µg EE/150 µg LNG
Days 85-91: 10 µg EE

The Applicant believes that the increases in EE will help minimize the incidence of unscheduled (breakthrough) bleeding and spotting, without increasing the total EE exposure.

2. Background

2.1 DESCRIPTION OF PRODUCT

LNG and EE are well-characterized progestin and estrogen products, respectively, that are widely used in combined hormonal contraceptive products. These products reduce the risk of pregnancy mainly via the effect of the progestin on suppressing ovulation, along with changes in cervical mucus that inhibit sperm motility and endometrial changes that may inhibit implantation. The estrogen component may make some contribution to the contraceptive action, and mainly acts to maintain cycle control and provide an acceptable bleeding profile.

The Applicant has several approved extended and traditional regimen COC products that contain EE and LNG. The dosage used in the phasic Quartette regimen is bracketed by that used in approved products. The annual EE and LNG exposure from Quartette is shown in

Table 1, which compares the exposure based on four 91-day cycles to that associated with use of other extended cycle COCs and a standard 21/7 regimen COC.

Table 1 Annual* Exposure to EE and LNG for Various COC Regimens

Drug and Regimen	EE	LNG
Quartette 91-day phasic cycles, including 7 days EE-alone	8.3 mg	50.4 mg
Seasonique 91-day cycles of EE 30 µg/LNG 150 µg for 84 days and 7 days EE-alone	10.4 mg	50.4 mg
LoSeasonique 91-day cycles of EE 20 µg/LNG 100 µg for 84 days and 7 days EE-alone	7.0 mg	33.6 mg
Nordette 28-day cycles of EE 30 µg/LNG 150 µg for 21 days and 7 day pill-free interval	8.2 mg	41.0 mg

*** Annual exposure based on four 91-day cycles per year and 13 28-day cycles per year**

2.2 REGULATORY HISTORY

The Applicant conducted the drug development program for this indication under IND 72,290, which was opened in 2006. A preIND meeting was requested in 2006, but the Applicant canceled the meeting request after receiving the Division's preliminary comments regarding the proposed phase 2 dose-finding study. The Division's advice included a request to enroll women with body mass index (BMI) up to 35 kg/m^2 and agreement on the proposed ascending doses to be evaluated. The phase 3 protocol was reviewed by the Division and no comments were sent to the Applicant.

Written responses in lieu of a meeting were provided in March 2012 when the Applicant requested preNDA guidance. The Division discussed the following issues:

- The primary analysis should be based on the Pregnancy Intent to Treat (PITT) population excluding all 28-day cycles in which other methods of birth control were used, unless a pregnancy occurred in such a cycle
- The proposed 28-day cycle Pearl Index calculation should be revised
- The Division agreed with the proposed presentation of bleeding data

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Vaishali Popat, stated in her review dated March 1, 2013:

Approval is recommended for this extended cycle oral contraceptive, Quartette.

Team Leader Comment:
I concur with Dr. Popat's recommendation.

Dr. Popat did not recommend any postmarketing risk evaluation and mitigation strategies or postmarketing requirements/commitments.

3. CMC/Device

3.1 CMC

Information about the drug substances (EE and LNG) was cross-referenced to two DMFs, which have been reviewed several times and determined to be adequate. The primary Chemistry Reviewer, Rajiv Agarwal, Ph.D., noted that the proposed tablets are nearly identical in formulation and manufacture to those of the currently approved tablets (differing only in the debossing code). The Applicant accepted Dr. Agarwal's recommended revision to the dissolution acceptance criteria. The stability data supported the requested 18 month expiry. At the time of Dr. Agarwal's review, agreement on labeling had not been met; therefore, he made the following recommendations in his review dated January 31, 2013:

> *This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.*
>
> *The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.*
>
> *However, the issues on the label/labeling of the drug product have **not** been resolved.*
>
> *Therefore, from the ONDQA perspective, this NDA is **not** recommended for approval per 21 CFR 314.125(b)(6) in its present form until label/labeling issues are satisfactorily resolved.*

No post-marketing commitments or risk management strategies were recommended.

Following submission of acceptable labeling, Dr. Agarwal submitted an addendum to his review on March 21, 2013, noting that CMC-related labeling issues had been resolved and carton/container labeling was acceptable. He made the following recommendation:

> *This NDA is now recommended for approval from the ONDQA perspective with expiration dating period of 18 months.*

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any preclinical studies for this NDA, but referenced the NDAs for its existing LNG/EE products (21-544, 21-840 and 22-262) to fulfill the requirements for nonclinical evaluation. The active drugs and excipients in these approved products are identical to those in the current NDA.

The primary Toxicology Reviewer, Krishan Raheja, D.V.M., Ph.D., made the following recommendations in his NDA review dated October 22, 2012:

> *Recommendations on approvability: P/T recommends approved of NDA 204061 for prevention of pregnancy.*
>
> *Additional Non Clinical Recommendations: None*
>
> *Recommendations on labeling: Sponsor has submitted draft labeling.*

5. Clinical Pharmacology/Pharmacometrics

5.1 Clinical Pharmacology

The Applicant cross-referenced the NDAs for the three approved extended cycle LNG/EE COCs (21-544, 21-840 and 22-262) for the clinical pharmacology information needed in this NDA. A single bioavailability study was submitted to the current NDA, to evaluate the pharmacokinetics (PK) of the three combination tablet strengths following a single administration of two tablets of each of the respective strengths (Study 101). This study found that LNG PK was within the 80-125% limits of bioequivalence for each of the three tablet strengths. For EE, there was a dose-proportional increase in Cmax and AUC as the EE dose increased over the three phasic tablet strengths.

The Applicant also conducted a phase 2 study that compared the bleeding profile of various different phasic regimens and of Seasonale, to identify the optimal regimen to study in phase 3. The three phasic regimens evaluated included the same three dose strengths, but differed only in the number of days a given dose strength was administered. The regimen taken into phase 3 was that considered to be the "low dose" regimen in the phase 2 study, because the lowest dose (20 µg EE/150 µg LNG) was used for the greatest number of days (42) in this regimen. The Applicant determined that the bleeding profile for the low dose regimen was slightly superior to that observed for Seasonale; given that the safety profiles were equivalent for all three dose regimens, the low dose was taken into phase 3.

Dr. al Habet stated the following in his review dated February 22, 2013:

From the Clinical Pharmacology perspective, this NDA is acceptable.

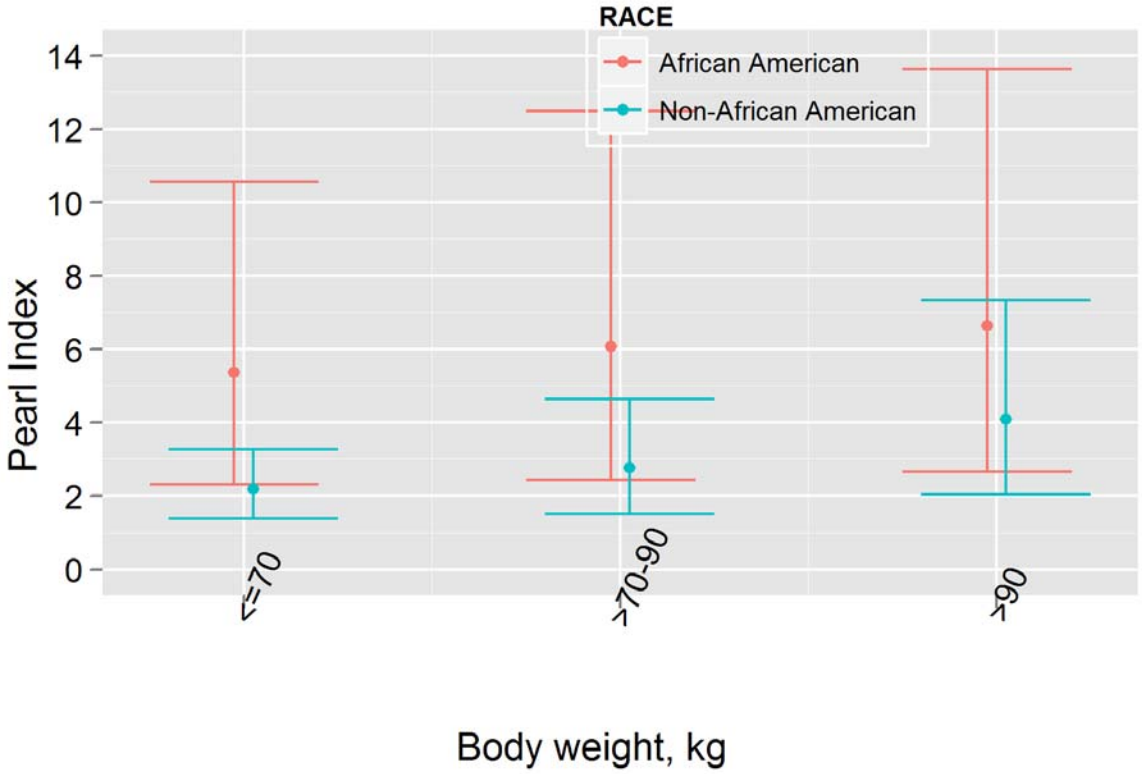
Dr. al Habet did not recommend any phase 4 requirements or commitments.

5.2 Pharmacometrics

The pharmacometrics reviewer, Jeffrey Florian, Ph.D., reviewed the Applicant's population PK model. He reached the following conclusions:

- Study 201 showed no distinct differences in the incidence of bleeding/spotting between the three phasic dose regimens evaluated
- The predicted EE exposure based on Study 101 falls between that of Seasonique and LoSeasonique
- Body weight > 90 kg and African American race were associated with an increased Pearl Index compared to that in thinner or non-African American women. The increase in African American women did not appear to be attributable solely to higher body weight (see Figure 1).

Figure 1 Pearl Index by Race and Body Weight



Source: Pharmacometrics review addendum by Jeffrey Florian, Ph.D., dated February 26, 2013

Team Leader Comment:
While the point estimates are consistently higher for African American women at every weight stratum, the 95% confidence intervals (CI) shown above overlap, and the relatively small sample size among African Americans is reflected by the imprecision of the point estimate. The impact of race and weight is explored further in Section 7.4.3.

6. Clinical Microbiology

No clinical microbiology consult was requested for this product.

7. Clinical/Statistical – Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The development program for Quartette included three studies, all conducted in the US: one relative bioavailability study, one dose-finding phase 2 study, and one open-label phase 3 study. These studies are briefly outlined in Table 2.

Table 2 Clinical Development Program for Quartette

Study ID	Design* Phase	Drugs/Doses	Objectives	N	Endpoints
Study 101	Single dose, three period cross-over Phase 1	Period 1: two tablets of 20 µg EE/150 µg LNG Period 2: two tablets of 25 µg EE/150 µg LNG Period 3: two tablets of 30 µg EE/150 µg LNG	Relative bioavailability of three different dosage strengths	18 enrolled	PK, safety
Study 201	MC, DB, R Two 91-day cycles Phase 2	Group 1: Low dose Group 2: Midrange dose Group 3: High dose Group 4: Seasonale	Dose regimen-finding	567 enrolled Group 1: 140 Group 2: 136 Group 3: 143 Group 4: 148	Bleeding/spotting days, safety
Study 301	OL, single arm Four 81-day cycles (one year) Phase 3	42 days of 20 µg EE/150 µg LNG 21 days of 25 µg EE/150 µg LNG 21 days of 30 µg EE/150 µg LNG 7 days of 10 µg EE	Safety and efficacy	3,701 enrolled, 3,597 treated	Pregnancy rate, safety, bleeding profile

*** MC = multicenter, DB = Double-blind, R = randomized, OL= open label**
Source: Based on Tabular Listing of Studies

7.1.1 Study 301

The single phase 3 study, Study 301 was a 12 month, single arm, open-label, multicenter trial that enrolled 3,701 sexually active women aged 18-40 years.

Entry criteria specified inclusion of sexually active women ages 18 to 40 years, with regular menstrual cycles and general good health. Exclusion criteria included smokers ≥ 35 years and other common exclusions for contraceptive trials that reflect contraindications to use of hormonal contraception. Women were enrolled without restriction on BMI.

Team Leader Comment:
The entry criteria were those generally utilized in hormonal contraception trials; however, per the Division's request, the Applicant did not impose a BMI restriction. The Division has been urging sponsors to avoid BMI restrictions, so the study populations will be more reflective of the general population, with the increasing burden of obesity.

Subjects started using the study drug on the first Sunday after the start of their menses ("Sunday start") and were instructed to take one tablet daily at about the same time each day. A daily diary was used to record pill intake, bleeding/spotting occurrence and severity, use of back-up contraception and any use of concomitant medications. Nonhormonal back-up contraception was used for the first seven days of Quartette use, when two or more consecutive pills were missed and when subjects used an intermittent drug known to interact with COCs (back-up required for the entire course of therapy plus seven days after discontinuation of the concomitant medication).

7.1.2 Study 201

The Applicant relied upon bleeding endpoints in phase 2 to select the dose regimen to take forward into phase 3. Study 201 was a double-blind, randomized, multicenter, two-cycle, four-arm trial in 567 women. The following arms were evaluated:

- Group 1 ("low dose") – **42 days** of 20 µg EE/150 µg LNG, then 21 days of 25 µg EE/150 µg LNG, then 21 days of 30 µg EE/150 µg LNG, then seven days of 10 µg EE alone
- Group 2 ("midrange dose") - 21 days of 20 µg EE/150 µg LNG, then **42 days** of 25 µg EE/150 µg LNG, then 21 days of 30 µg EE/150 µg LNG, then seven days of 10 µg EE alone
- Group 3 ("high dose") - 21 days of 20 µg EE/150 µg LNG, then 21 days of 25 µg EE/150 µg LNG, then **42 days** of 30 µg EE/150 µg LNG, then seven days of 10 µg EE alone
- Group 4 (Seasonale) – 84 days of 30 µg EE/150 µg LNG, then seven days of placebo

Bleeding profile results from Study 201 are presented and the study is discussed more fully in Dr. Popat's review, but is not reviewed further here.

7.2 DEMOGRAPHICS

Table 3 shows the demographics of the Safety population in Study 301 which is defined as all randomized subjects who received any amount of study drug.

Table 3 Study 301 – Demographics and Baseline Characteristics – Safety Population

Variable	N=3,597
Age (years; mean (SD) and range)	27.1 (5.7) 18-41
≤ 35 years (N, %)	3,152 (87.6)
> 35 years (N, %)	445 (12.4)
Weight (lb; mean (SD) and range)	162.5 (43.2) 83-402
BMI (kg/m^2; mean (SD) and range)	27.4 (7.0) 15.5-64.7
< 30 (N, %)	2,569 (71.4)
≥ 30 (N, %)	1,027 (28.6)
Race/ethnicity (N, %)	
White (non-Hispanic)	2,324 (64.6)
Hispanic or Latina	404 (11.2)
Black	696 (19.3)
Asian	78 (2.2)
Other	95 (2.6)
Previous hormonal contraceptive use (N, %)	
New user (naïve, no prior history)	619 (17.2)
Continuous user (use immediately prior to study drug)	1,570 (43.6)
Prior user (prior use, but not current use)	1,408 (39.1)

Source: Based on Applicant's Report for Study 301, Table 6, pp 54-55 and Dr. Guo's analyses

Team Leader Comments:

- **The proportion of women > 35 years is sufficient to provide safety data on this subpopulation; they are not included in the primary efficacy population.**
- **The weight/BMI distribution is similar to other recent US trials in which entry criteria have not restricted heavier women.**

- **Current Census figures[1] report that the US population comprises 64% Non-Hispanic Whites, 16% Hispanics, 13% African-Americans, 5% Asians and 7.1% "other." By this measure, the Applicant enrolled slightly higher percentages of African-Americans, and slightly lower percentages of Hispanics, Asians and "others" compared to the US population.**

7.3 DISPOSITION OF SUBJECTS

The overall study completion rate was about 60% (see Table 4), and the most common reasons for premature discontinuation were loss to follow-up and adverse events (AEs).

Table 4 Study 301: Disposition of Subjects

	Overall	Excluding Site LA0012
Number Enrolled	3,701	3,667
Number Treated	3,597 (100%)	3,565 (100%)
PITT population n (%*)	3,019 (83.9%)	2992
Discontinued n (%*)	1,453 (40.4%)	1,421(40.9%)
Primary Reason for Discontinuation n (%*):		
Adverse Event	466 (13.0%)	457(12.8%)
-bleeding and/or spotting related	167 (4.6%)	162 (4.5%)
Lost to Follow-up	480 (13.3%)	472 (13.2%)
Non-compliant	137 (3.8%)	137 (3.8%)
Investigator Discretion	5 (0.1%)	5 (0.1%)
Pregnancy	68 (1.9%)	68 (1.9%)
Protocol Violation	16 (0.4%)	16 (0.5%)
TEVA Requested Subject's Withdrawal	35 (1.0%)	21 (0.6%)
Subject Request to be Withdrawn	217 (6.0%)	216 (6.1%)
Other	29 (0.8%)	29 (0.8%)

*Denominator for % calculation is the number treated.
Source: Table 2, Statistical review by Dr. Guo, dated February 22, 2013, based on Table 3, CSR and Dr. Guo's calculations

Team Leader Comments:

- **The Applicant notes that four subjects withdrew for AEs that were not treatment-emergent, and one subject who withdrew due to an AE was not identified in the listing above. Therefore, the number of women who withdrew due to a treatment-emergent AE is 463, as displayed in Table 13.**
- **As noted previously, 14 subjects were prematurely terminated by the Applicant when site LA 0012 was closed for GCP violations.**
- **Excluding the site LA 0012 subjects, the Applicant requested withdrawal of an additional 21 subjects. Review of the line listings identifies noncompliance, no longer sexually active, protocol violations/use of prohibited medications and unspecified sponsor decision as the primary reasons underlying withdrawals in this category.**
- **Dr. Popat reviewed the "subject request" category for withdrawal and identified 15 subjects who actually reported an AE associated with the decision to withdraw. The**

[1] 2010 Census Shows America's Diversity, http://www.census.gov/2010census/news/releases/operations/cb11-cn125.html, accessed January 25, 2013. Numbers sum to > 100% because data on Hispanic ethnicity was collected by a separate questionnaire than that used to determine race; Hispanic ethnicity is not included in the 5 racial groups tabulated by Census, and Hispanics may be of any race.

most frequent of these AEs was a bleeding complaint (11 subjects), followed by acne (2 subjects) and weight gain and migraine (1 subject each).

- **Overall, the rate of completion and discontinuations due to loss to follow-up, AEs, and subject request is within the range commonly observed in other year-long contraception trials.**

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

Primary Endpoint

The primary efficacy endpoint was the Pearl Index based on all on-drug pregnancies in women aged 18 to 35 years. Evaluable cycles were those in which no methods of back-up contraception were used (and any cycle in which a conception occurred was considered evaluable). The Pearl Index was calculated for both 91-day cycles and 28-day cycle equivalents. Partial cycles in which a pregnancy was conceived were considered complete cycles.

On-drug pregnancies were defined by FDA as all pregnancies for which the conception date was determined to be on drug or within seven days after the last tablet (whether combination or EE-alone tablet).

Team Leader Comments:

- **The Division prefers to use 28-day cycle equivalents even for extended cycle regimens, because this shorter interval results in less loss of data from "unevaluable cycles." If a 91-day cycle is used, even a single use of back-up contraception renders that entire 91-day cycle unevaluable; while using a 28-day cycle equivalent, only 28 days of data would be considered unevaluable.**
- **The Applicant originally counted the "seven day window" of conception based on last active tablet. After being reminded in the filing letter of the Division's convention, the Applicant recalculated the Pearl Index to include pregnancies conceived within seven days after the EE-alone tablet as well.**

Subjects had either a clinic visit or telephone contact approximately every four weeks during the study. Serum pregnancy testing was done at each visit and was to be done by subjects if they suspected they might be pregnant. In case of a positive urine pregnancy test at home, the subject was to come into clinic for a serum test and a vaginal ultrasound if positive.

Team Leader Comment:

The primary efficacy endpoint is that used in contraception trials. Appropriate exclusions were made of cycles in which back-up contraception was used.

7.4.2 Primary Efficacy Analysis

The primary endpoint upon which the Division relied was the 28-day cycle equivalent Pearl Index, calculated as:

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment*}}$$

* Only cycles in which subjects used no back-up contraceptive methods were included.

The primary analysis population was based on the PITT population, defined as all subjects aged 18-35 years who completed at least one 28-day cycle equivalent. Partial cycles in which a pregnancy was conceived were considered complete cycles. The Applicant also

calculated pregnancy rates and Pearl Indices for subsets based on body weight < 90 kg and ≥ 90 kg. A post hoc analysis by BMI was also conducted.

7.4.3 Primary Efficacy Results

The Applicant reported a total of 84 pregnancies to women enrolled in the trial, and initially reported a total of 65 on-treatment pregnancies among women in the PITT population. However, this was based on including a window of seven days after the last combination pill; when reminded that the Division includes seven days after the last tablet (including EE-alone), the Applicant agreed to add two pregnancies conceived within this window, giving a total of 67 on-drug pregnancies. Of the 84 total pregnancies, four had no outcome information mentioned, 23 were lost to follow-up and 57 had some information on pregnancy outcome. Of this latter group, 26 had a term infant, five had a premature infant, two had an ectopic pregnancy, six had a spontaneous abortion, one had a missed abortion, one had a D&C for a non-viable pregnancy and 16 had an elective abortion.

As with any contraception NDA, the clinical reviewers evaluated all potential pregnancies, including those that were not confirmed because the subject was lost to follow-up and those considered by the Applicant to have occurred pre- or post-treatment. Based on this review, Dr. Popat identified three additional on-treatment pregnancies. Two were identified based on estimated dates of conception that differed from that calculated by the Applicant; according to the Division's calculations, the conception date fell just within the 7-day window. An additional case involved a subject who was lost to follow-up, without confirmation or dating of her self-reported pregnancy. When the Division reviews potential on-treatment pregnancies, it typically uses a "worst case" scenario approach, in which cases that are missing information that would allow for a conclusive determination are considered "on-treatment" pregnancies. This is done because it is known that the pregnancies reported in a trial may be under-estimates; for example, pregnancy status is unknown for subjects lost to follow-up, but it is certainly possible that some subjects who stop communicating with a study site have become pregnant. Details of these additional pregnancies considered on-treatment by the Division are shown in Table 5.

Table 5 Study 301: Details of Additional On-Treatment Pregnancies Identified by FDA

Subject ID	Applicant's Designation	Last Drug Use	Conception Date	Basis for diagnosis/dating; other comments
001/115	Off-drug	Unknown; Applicant estimated as 10/23/10	10/30/10	Subject attended her last study visit on 8/18/10, one month into the study. She phoned the study site on 1/3/11 to report a positive home pregnancy test on 12/20/10. She was then lost to follow-up. Subsequent review of her obstetrical records revealed that she had had an ultrasound on 11/30/10 that revealed a fetus with an estimated gestational age (EGA) of 6 3/7 weeks, giving an estimated date of conception of 11/1/10 per the Applicant. The woman had an elective abortion in (b) (6). The Applicant stated the estimated conception date as 11/1/10, which would fall just outside the 7-day window. However, verification of dates with a calendar gives a conception date of 10/30/10, within the window.
005/055	Unconfirmed	Unknown; Division estimated as 5/1/11	Unknown	Subject last seen on 1/24/11, but phoned to report a positive pregnancy test on 4/4/11. She was then lost to follow-up. Counted under "worst-case" scenario because the subject had a supply of Quartette sufficient to last until 5/1/11, or post-conception.
042/029	Off-drug	1/19/10 per subject	1/26/10	Subject reported last pill taken 1/19/10. Ultrasound on 3/18/10 gave an EGA of 9 2/7 weeks, with an estimated date of conception of 1/27/10 per the Applicant, which fell just outside the 7-day window. However, verification of date with a calendar gives a conception date of 1/26/10, just within the window.

The overall temporal distribution of conceptions relative to study drug use in Study 301 is shown in Table 6.

Table 6 Timing of Conception

	Study 301	
Timing of conception	**N**	**Comment**
Total # pregnancies	84	
Prior to starting treatment	6	3 of these subjects never started Quartette
On treatment	**63**	
≤ 7 days after last pill	**5**	**(includes 2 of the pregnancies added by the Division)**
Unknown last intake	**2**	**(includes 1 of the pregnancies added by the Division)**
> 7 to ≤ 14 days after last pill	2	
> 14 days after last pill	5	Occurred 19 to ~ 60 days after last dose
Other pregnancies not counted	1	Occurred in a 38 year old, not in PITT

Team Leader Comments:

- **Two cases were determined by the Division to represent on-drug pregnancies because the Division's dating per a standard obstetric wheel provided an estimated date of conception that was a day or two earlier than that identified by the Applicant, which moved the conception into the seven-day window after last drug use. Although wheels are somewhat imprecise, my own calculations using**

a calendar confirmed Dr. Popat's calculations. In addition, Subject 042/029 stopped her drug use mid-cycle, which increases the likelihood of an on-drug pregnancy.

- **One other pregnancy may have occurred on-treatment. Subject 075/006 took her last dose on 11/13/10 and had a positive pregnancy test at her final study visit on 12/8/10. An ultrasound was done that day and the narrative reported that the EGA of the fetus was 6 0/7 weeks. This would have given an estimated conception date of 11/10/10, or on-treatment. However, the CRF reported an EGA of 4 weeks. The Applicant was asked to provide a copy of the ultrasound to resolve the discrepancy; the report was a single page, hand-written statement (b) (6) The size of the gestational sac plus the absence of a fetal pole suggests an EGA of about 5 weeks, which would make the conception date 11/17/10. By six weeks, a fetal pole would typically have been observed. The subject went on to have an abortion. However, the addition of this additional pregnancy would not change the Pearl Index substantially, so I am willing to accept the Applicant's assertion that it occurred more than seven days post-drug.**
- **The Applicant was informed of the three additional on-drug pregnancies considered by the Division in the Pearl Index calculation, and accepted the Division's determination.**

Pearl Index

The statistical reviewer, Jia Guo, Ph.D., calculated Pearl Indices based on both 28-day cycle equivalents and 91-day cycles. Her calculations using 28-day cycle equivalents, which include the additional pregnancies identified by the clinical reviewers, are shown in Table 7, along with the original Applicant calculations.

Table 7 Pearl Index Calculation, Based on 28-day Cycle Equivalents, PITT Population*

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of Cycles using Backup Contraception	Number of Evaluable Cycles	Pearl Index	95% CI
Applicant	2,992	67	30,363	1,848	28,515	3.05	(2.37, 3.88)
Reviewer	2,992	70	30,363	1,848	28,515	**3.19**	**(2.49, 4.03)**

***Site LA0012 is excluded.**
Source: Table 3, Statistical review by Jia Guo, Ph.D., dated February 22, 2013

Team Leader Comment:
As expected, due to the lower number of evaluable cycles, the Pearl Index was higher when based upon 91-day cycles (3.52 with an upper bound of the 95% CI of 4.44).

Several sensitivity analyses were conducted to address the possible impact of specific sites on the efficacy results. Dr. Guo evaluated the Pearl Index with and without the two sites at which the investigators had financial disclosures (total N = 160). Although excluding these two sites resulted in excluding three pregnancies from the Pearl Index calculation, the overall impact on the Pearl Index was minimal. Dr. Guo also evaluated the impact on the Pearl Index of including Site LA 0012, which was terminated by the Applicant during the course of the study. This site enrolled 34 subjects, 20 of whom had discontinued due to AEs by the time the Applicant terminated the site. The remaining 14 subjects were discontinued when the site was closed. The site was terminated due to irregularities and GCP deficiencies noted by the Applicant during monitoring visits. No pregnancies occurred at this site, and a total of

155 cycles of treatment data were contributed by the subjects at this site. Results of these sensitivity analyses are presented in Table 8.

Table 8 Sensitivity Analyses of Pearl Index

Sensitivity Analysis	28-day cycle equivalent Pearl Index	95% Confidence Interval
Excluding two sites with financial disclosures (071 & 082)	3.15	2.45, 3.99
Including Site LA 0012	3.17	2.48, 4.00

Source: Calculations by Dr. Guo, statistical reviewer

Dr. Guo also looked at efficacy in subgroups by race (see Table 9) and body weight (see Table 10). Age and region were not explored because the study only enrolled reproductive-aged women and was conducted in the US only.

Table 9 Pearl Index by Race, Based on 28-day Cycle Equivalents, PITT Population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of Cycles using Backup Contraception	Number of Evaluable Cycles	Pearl Index	95% CI
White	1,952	40	20,228	1,144	19,084	2.72	(1.95, 3.71)
Black or African American	548	22	5,186	381	4,805	5.95	(3.73, 9.00)
Other	492	8	4,949	323	4,626	2.25	(0.97, 4.43)

Site LA0012 is excluded.
Source: Table 5, Statistical review by Jia Guo, Ph.D., dated February 22, 2013

Team Leader Comments:

- **Although there appear to be some racial disparities in Pearl Indices, the 95% confidence intervals are quite wide for the non-white subgroups. For Blacks, the lower bound excludes the upper bound for White women.**
- **The Applicant was asked to address the racial disparity, and responded that it was due to the higher weight in the Black subgroup. However, as demonstrated in Dr. Florian's analysis, shown in Figure 1, this is not an adequate explanation. The Applicant further noted that the assessment of the impact of race on systemic exposure to EE indicated little difference in median systemic exposure across races.**
- **A larger study, specifically powered to evaluate racial/ethnic differences would be needed to make any definitive statements about any impact of race/ethnicity on efficacy.**
- **Similar findings have been observed in other US contraception trials and the reasons for racial differences have not been elucidated. Compliance with the dose regimen may be part of the explanation; however, it is likely that race is a surrogate for other factors (e.g., education, socioeconomic status) that may influence compliance or otherwise impact effectiveness.**

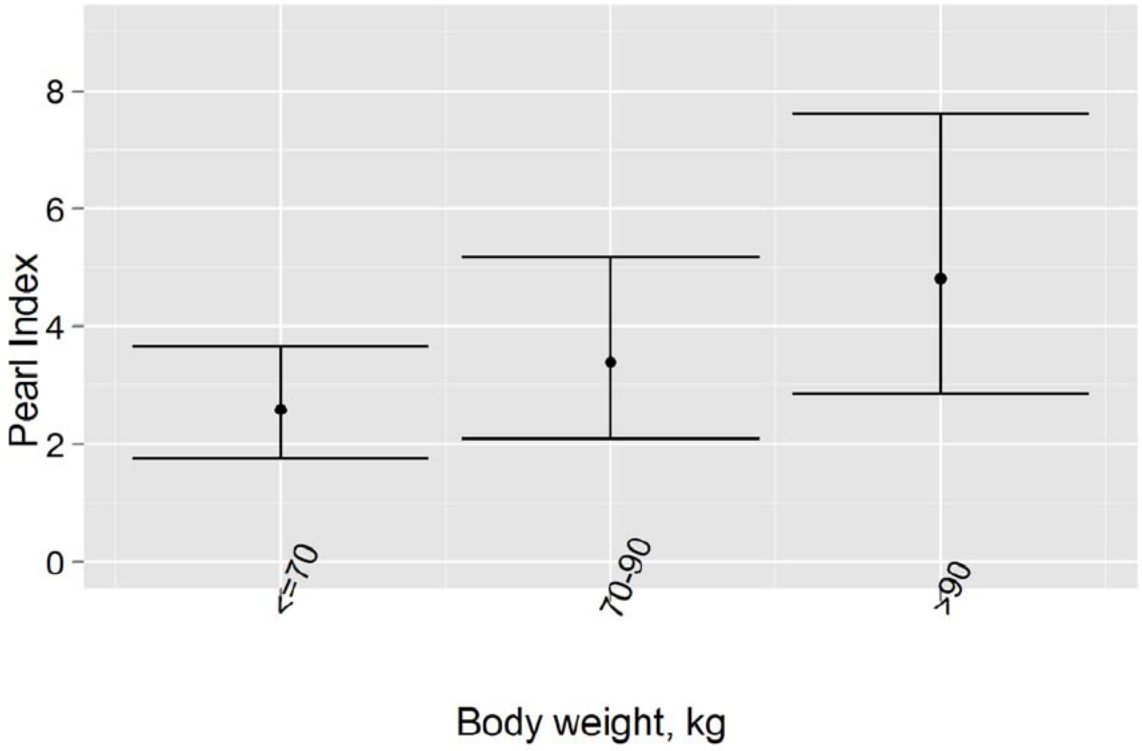
Table 10 Pearl Index by Body Weight, Based on 28-day Cycle Equivalents, PITT Population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of Cycles using Backup Contraception	Number of Evaluable Cycles	Pearl Index	95% CI
< 90 kg	2,457	52	25,169	1,512	23,657	2.86	(2.13, 3.75)
≥ 90 kg	535	18	5,194	336	4,858	4.82	(2.86, 7.60)

Site LA0012 is excluded.
Source: Table 7, Statistical review by Jia Guo, Ph.D., dated February 22, 2013

Dr. Florian also explored the effect of body weight on efficacy, using slightly different weight categories. His results are shown in Figure 2. Based on the Applicant's population PK, Dr. Florian stated that given the identified impact of body weight on EE exposure, he "questions whether the lowest dose in the current regimen and the already approved LoSeasonique will provide sufficient exposures for subjects with body weights > 90 kg. However, the information available from the current submission is insufficient to address this question."

Figure 2 Pearl Index by Body Weight



Source: Pharmacometrics review addendum by Jeffrey Florian, Ph.D., dated February 26, 2013

Team Leader Comment:
In both analyses, there is a trend for increasing Pearl Index with increasing body weight. However, using either categorization, the 95% confidence intervals overlap. At this time, I do not believe we have sufficient reason to describe differential efficacy by weight in labeling.

Statistician's Conclusion

Dr. Guo identified two potential statistical issues in the application. These were a discrepancy between the Division's convention and the Applicant's definition of on-drug pregnancies, and the impact of the terminated site, LA0012 on safety and efficacy data. Dr. Guo included in her analyses the additional pregnancies identified by the clinical reviewer, and excluded data from Study LA0012. She made the following conclusions and recommendations regarding contraceptive efficacy in her review dated February 22, 2013:

> *From a statistical perspective, the study results supported the efficacy of Quartette, an oral regimen of levonorgestrel (LNG)/ethinyl estradiol (EE)…, in the prevention of pregnancy. The effectiveness of Quartette appeared to be attenuated in Blacks and in women with a body weight ≥ 90 kg.*

7.4.4 Secondary Efficacy Analysis - Bleeding Profile

The total number of bleeding and/or spotting days during each 84-day active treatment cycle (defined as unscheduled bleeding) and each seven-day withdrawal cycle (defined as scheduled bleeding) were considered safety endpoints in Study 301. Subjects completed a daily diary for each cycle that recorded occurrence and intensity of bleeding or spotting. Spotting was defined as use of < one tampon/pad per day; bleeding was defined as any bloody discharge requiring use of at least one tampon/sanitary napkin per day. Definitions provided to distinguish intensity of bleeding were as follows:

- None – no vaginal bleeding
- Light – 1-2 tampons/pads per day
- Moderate – 3-5 tampons/pads per day
- Heavy – 6+ tampons/pads per day

Team Leader Comments:

- **The definition of "spotting" is rather unclear, but presumably refers to bleeding that requires no greater protection than a panty liner, which is a commonly used definition used for spotting.**
- **Most commonly, bleeding intensity definitions are characterized in relation to the subject's usual menstrual pattern (e.g., lighter, similar to or heavier than her usual menses). The definitions used here may be more impacted by subjects' personal habits (i.e., some women may change their sanitary protection after each bathroom visit, rather than on a schedule dictated by the bleeding intensity). However, the Division has typically not given great consideration to the intensity dimension of the bleeding profile; rather, it has focused more on frequency of bleeding/spotting.**

The Applicant reported bleeding profile information based on the Intent to Treat (ITT) population, defined as all subjects who took study drug for at least 28 days. Bleeding data from incomplete cycles were excluded from analysis; however, upon the Division's request, the Applicant provided data that included all women who completed at least one 28-day cycle equivalent. Table 11 presents unscheduled bleeding and spotting data from Study 301 by 91-day cycles for this group of subjects.

Table 11 Study 301: Total Number of Unscheduled Bleeding and/or Spotting Days per 91-day Cycle

Cycle	N	Days per 84-Day Interval				Median Days Per Subject-Month
		Mean (SD)	Q1	Median	Q3	
1	3,300	17.8 (16.3)	5	14	27	3.5
2	2,798	10 (12.5)	1	5	14	1.3
3	2,420	7.7 (12.1)	0	3	10	0.8
4	2,208	6.6 (10.8)	0	3	8	0.8

Source: Applicant's response to Division's Information Request, submitted December 21, 2012, Table 26_28, p 81

Team Leader Comments:

- **Due to the Sunday start, women may have been finishing their prior menses at the beginning of Cycle 1; for this reason, the number of days of unscheduled bleeding captured for Cycle 1 may be spuriously high.**
- **The Applicant also characterized unscheduled bleeding/spotting by the phase within a treatment cycle; data from Cycles 2-4 demonstrates that unscheduled bleeding/spotting tended to be higher during the 42 days during which the women received the lowest EE dose.**
- **Overall, from Cycles 2-4, the frequency of unscheduled bleeding/spotting appears similar to that observed with other extended cycle regimens, and is likely to be acceptable to the majority of women.**

After cycle 1, the proportion of women with no unscheduled bleeding/spotting during a treatment cycle increased, from about 20% in Cycle 2 to 32% in Cycle 4. Scheduled bleeding/spotting lasted a mean of about three days per cycle (median of 3-4 days).

Team Leader Comment:
The overall bleeding profile appears acceptable, although it is not evident that the phasic regimen has demonstrated the desired reduction in unscheduled bleeding/spotting compared to other, monophasic, extended cycle regimens.

7.4.5 Overall Assessment of Efficacy

The data in the phase 3 study provides acceptable evidence of efficacy to warrant approval of this NDA for prevention of pregnancy. Although the Pearl Index is slightly higher than previously approved (the prior high Pearl Index was 2.92), the upper bound of the 95% confidence interval is well within the range of those in other approved products (typically ≤ 5.0). The Applicant and the Division were in reasonable agreement on the number of on-drug pregnancies (it is common that the Division identifies a few more than do Applicants).

The impact of race and higher body weight on efficacy continues to be problematic in contraception trials. Studies that do not restrict enrollment on the basis of BMI or body weight have commonly demonstrated higher Pearl Indices among heavier women, although the number of such subjects is usually insufficient to result in a statistically significant difference. Similarly, it is not unusual to find racial discrepancies in the Pearl Index calculations, although again, confidence intervals are usually wide and overlapping among subgroups. At this time, I do not believe we have sufficient data to warrant description of these effects in labeling.

The demonstrated bleeding profile was acceptable.

8. Safety

The safety database evaluated by Dr. Popat in her review included data from the phase 2 and the phase 3 studies. Because the number of women on the to-be-marketed regimen in Study 201 was small relative to that in Study 301, and because Study 201 ran for only six months, I will focus my review on data from Study 301, with reference to Study 201 where noted.

Overall, the phase 2 and phase 3 studies included 4,164 women on the to-be-marketed treatment regimen. In Study 301, 2,183 women (61%) completed the full course of 13 28-day cycle equivalents, providing a total of over 28,000 28-day cycle equivalents of exposure. Including women who did not complete the full study, Study 301 provided over 34,000 cycles of exposure.

Team Leader Comment:
The Applicant exceeded the Division's usual request for 10,000 28-day cycle equivalents and 200 women completing a year of treatment

8.1 DEATHS AND SERIOUS ADVERSE EVENTS

Deaths

There were no deaths in the clinical development program.

Serious Adverse Events

Serious adverse events (SAEs) occurred in 58 women in Study 301 (1.6%). The listing of SAEs excluding those unlikely to be at least possibly drug-related (e.g., excluding infections and orthopedic problems) is shown in Table 12.

Table 12 Possibly Drug-Related SAEs in Study 301

	N = 3,597	
	n	%
Total	58	1.6
System Organ Class (Preferred Term)		
Vascular disorders	**4**	**0.11**
Deep vein thrombosis **	3	0.08
Pulmonary embolism	1	0.03
Pregnancy, puerperium and perinatal conditions*	**10**	**0.28**
Abortion, spontaneous	5	0.14
Abortion, missed	1	0.03
Blighted ovum	1	0.03
Ectopic pregnancy	2	0.06
Premature separation of placenta	1	0.03
Nervous system disorders	**3**	**0.08**
Convulsion*	3	0.08
Cardiac disorders	**3**	**0.08**
Supraventricular tachycardia	1	0.03
Angina pectoris*	1	0.03
Atrial fibrillation	1	0.03
Hepatobiliary disorders	**5**	**0.14**
Cholecystitis	3	0.08
Cholelithiasis	2	0.06
Gastrointestinal disorders	**3**	**0.08**
Abdominal pain	3	0.08
Psychiatric disorders	**8**	**0.22**
Depression, suicidal*	1	0.03
Depression/suicide attempt	1	0.03
Anxiety	1	0.03
Suicide attempt**	4	0.11
Mental status changes*	1	0.03

*** Subject(s) discontinued due to SAE**
Source: Applicant's Study Report for Study 301 Table 22, pp 78-84

Team Leader Comments:

- **The overall rate of SAEs is consistent with that in other US contraception trials.**
- **Cholecystitis has been associated with hormonal contraception and is described in class labeling. The three cases reported here occurred after two, four, and five months on Quartette. One case was associated with cholelithiasis; she was discontinued from the study for noncompliance a month after her laparoscopic cholecystectomy. The other two subjects also underwent laparoscopic cholecystectomy. One case of cholecystitis was coded as cholelithiasis, but stones are not mentioned in the narrative. She underwent laparoscopic cholecystectomy after almost 11 months on Quartette. The other case of cholelithiasis occurred six months after starting Quartette and was considered related. The subject had discontinued study drug due to bleeding complaints two weeks before her SAE.**
- **The four venous thromboembolic events include one case (pulmonary embolus)**

that actually occurred on YAZ, six weeks after Quartette was discontinued. Of the three cases temporally associated with Quartette, one was also associated with recent orthopedic surgery (although the DVT site was unrelated to the surgical site); the other two did not have apparent risk factors beyond use of a COC.

- **Subject 036/008 had surgery on her right hip for excision of heterotopic ossification and IT band lengthening, and developed diaphoresis, shortness of breath and chest pressure on postop day (b) (6). She was diagnosed with a right basilica venous and right radial venous thrombosis; no lower extremity thromboses or pulmonary emboli were detected. According to the Applicant, the investigator did not initially recognize that she had had a DVT, and she was continued on study medication. By the time the VTE was recognized, she was allowed to complete the remaining two weeks of study drug.**
- **Subject 039/037 entered the study as a continuous COC user, having previously used YAZ. She developed an extensive DVT involving the left iliac, common femoral and greater saphenous veins 18 days after starting Quartette. She was discontinued from the study. Switching contraceptives after a break of four or more weeks is known to increase the risk of VTE, but it is interesting that this occurred in a woman who apparently had continuously used COCs.**
- **Subject 069/010 had a DVT of the left peroneal vein six months after starting Quartette; she had previously used COCs. She discontinued study drug.**
- **Subject 092-024 was a continuous user, having used YAZ before starting Quartette. She discontinued Quartette after 2 months due to worsened acne, and restarted YAZ. Six weeks later, she was diagnosed with a pulmonary embolus. Evaluation for Factor V Leiden was negative.**

- **The six cases of suicidality are somewhat surprising, even though depression is described in class labeling. Several of the cases apparently had prior psychiatric diagnoses, not all of which were disclosed at screening.**
  - **Subject 040/008 was seen in the ED for depression four months after starting Quartette. She admitted having ingested multiple Prozac and Klonopin pills in a suicide attempt. She disclosed a history of previous depression and suicidal ideation and noted that a child custody case had precipitated the current event. She was transferred to a behavioral unit and subsequently lost to follow-up.**
  - **Subject 051/054 had used Quartette for eight months before being hospitalized after an attempted self-strangulation. She had also attempted an overdose with ibuprofen several weeks earlier. Shortly after her discharge from the psychiatric facility she overdosed with 50 Haldol, but denied that this was a suicide attempt. She was rehospitalized briefly, but completed the study.**
  - **Subject 053/086 attempted suicide a year after starting Quartette, ingesting large quantities of alcohol and prescription pain and psychiatric medications. She was reported to have a history of bipolar disorder. She completed the study (her last use of study drug was on the day of the suicide attempt).**
  - **Subject 092/012 overdosed on ibuprofen and cough syrup (b) (6) days after starting Quartette. She was sent to a crisis center and started on Abilify and then Prozac for depression. She was discontinued from the study due to the suicide attempt.**

- **Subject 092/017 had been taking Quartette for three months when she made superficial cuts to her wrist and took alcohol and several sedatives and went to bed. She reported sadness and suicidal thoughts to the investigator the next day and went to the ED where she was admitted for observation. At that time, she "admitted she was not trying to kill herself." She discontinued the study.**
- **Subject 095/019 had a history of depression, and was taken to the ED one month after starting Quartette, having ingested a large amount of alcohol and multiple doses of Concerta and Klonopin. She was admitted with a diagnosis of worsening depression and suicidal ideation. She was discharged and subsequently lost to follow-up.**

- **The subject with mental status changes experienced confusion and lethargy 11 months after starting Quartette, and was felt to be postictal in the ED. She had an elevated prolactin level, but labs, head CT and EEG were otherwise normal. She recovered and was discharged, and discontinued study drug.**
- **The three cardiac events were determined not to be drug-related by the investigator. The case of angina in a 36 year old woman who used Quartette for two months was associated with exertion; the subject had a normal EKG, but slightly elevated CPK and troponin levels. She discontinued Quartette. The case of atrial fibrillation was felt to be related to dehydration and resolved with cardioversion. The supraventricular tachycardia had a normal cardiac and DVT/PE workup and she was discharged on Xanax.**

8.2 OTHER ADVERSE EVENTS

8.2.1 AEs leading to Discontinuation

The Applicant reported that 463 women in Study 301 discontinued prematurely due to a treatment-emergent AE. However, when the additional AE-related discontinuations identified by Dr. Popat are included, the AE discontinuation rate rises to 13.3% (478 women). Table 13 displays AEs that led to early withdrawal in more than one subject, and includes the additional subjects identified by Dr. Popat as having an AE-related discontinuation.

Table 13 AEs leading to Premature Withdrawal in > 1 Subject, Study 301

	N=3,597	
	n	%
Total	**478**	**13.3**
Preferred Term (PT)	**n for each PT**	**Aggregate for all PTs**
Metrorrhagia, vaginal hemorrhage, menorrhagia, menometrorrhagia, uterine hemorrhage; other bleeding	105, 54, 8, 1, 1, 11	5.0
Mood swings, mood altered, affect lability	25, 17, 9	1.4
Weight increased, other weight concern	44, 1	1.3
Headache, migraine, migraine with aura, other H/A	31, 15, 1, 1	1.3
Acne, acne cystic, other acne concern	34, 1, 2	1.1
Nausea, vomiting	28, 2	0.8
Blood pressure increased, hypertension, other BP concern	8, 8, 1	0.5
Depression, depressed mood, crying	12, 1, 3	0.4
Abdominal distension, discomfort	8, 4	0.3
Fatigue, sluggishness, asthenia	8, 2, 1	0.3
Decreased libido, loss of libido	8, 1	0.3
Abdominal pain, abdominal pain lower	4, 4	0.2
Anxiety, panic attack	7, 1	0.2
Irritability	8	0.2
Alopecia	7	0.2
Breast tenderness	7	0.2
Chest pain, chest discomfort	4, 2	0.2
Dizziness, dizziness postural, syncope, vertigo	3, 1, 1, 1	0.2
Dyspareunia, vulvovaginal dryness	2, 2	0.1
Vision blurred, visual impairment, myopia	2, 1, 1	0.1
Chloasma, pigmentation disorder	2, 1	0.08
Edema peripheral, swelling, fluid retention	1, 1, 1	0.08
Palpitations	3	0.08
Breast enlargement, breast swelling	1,1	0.06
Deep vein thrombosis	2	0.06
DUB	2	0.06
Emotional disorder	2	0.06
Ovarian cyst, hemorrhagic cyst	1, 1	0.06
Suicide attempt	2	0.06

Source: Based on Study Report for Study 301, Table 23, pp 85-8

Team Leader Comments:

- **The Applicant notes that the events coded as "vaginal hemorrhage" were mild to moderate in severity and associated with verbatim terms ranging from mild spotting to heavy bleeding. No subjects experienced significant change in hematologic indices or needed transfusion.**
- **The rate of discontinuations due to bleeding appears to be higher than that in other recent contraception trials (generally ≤ 3%).**

8.2.2 Common AEs

The Applicant reported that 2,605 women (72%) experienced one or more treatment-emergent AE during Study 301. However, the Applicant provided only a table listing the common AEs that occurred in ≥ 5% of subjects and a table listing AEs determined by the investigator to be treatment related that occurred in ≥ 2% of subjects. Information on less frequently occurring AEs was available only in individual subject line listings. For this reason, I am relying on Dr. Popat's analysis of phase 3 data. AEs that are likely to be drug-related and that occurred in ≥ 2% of subjects (when like terms are grouped together) are displayed in Table 14.

Table 14 Common Adverse Events Occurring in ≥ 2% of Subjects, Study 301

	N=3,597	
	n	%
Total Treatment-Emergent AEs	**2,605**	**73.8%**
Preferred Term (PT)	**n for each PT**	**Aggregate for all PTs**
Headache, migraine, tension headache, migraine with aura	427, 67, 21, 2	14.4
Metrorrhagia, vaginal hemorrhage, menorrhagia, menometrorrhagia, uterine hemorrhage	216, 112, 18, 2, 2,	9.7
Nausea, vomiting	242, 74	8.8
Vulvovaginal mycotic infection, fungal infection, vulvovaginal candidiasis, vaginal infection, candidiasis, vulvovaginitis	141, 86, 33, 20, 9, 3	8.1
Acne, acne cystic	193, 2	5.4
Dysmenorrhea	194	5.4
Weight increased	167	4.6
Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal tenderness	77, 45, 41, 1	4.6
Mood swings, mood altered, affect lability, emotional disorder, emotional distress	57, 42, 28, 3, 1	3.6
Depression, depressed mood, crying, major depression, affective disorder, depression suicidal, dysthymic disorder	91, 5, 3, 2, 1, 1, 1	2.9
Abdominal distension, discomfort	53, 42	2.6
Anxiety, panic attack	83, 3	2.4
Breast tenderness, breast pain, breast discomfort	73, 5, 1	2.2
Fatigue, sluggishness, somnolence, asthenia	64, 2, 2, 5	2.0

Source: Based on MAED analysis by Dr. Popat, Medical Reviewer

Team Leader Comment:
The rate of "any AE" is consistent with typical rates in 12-month trials (70-80%) and the types of common AEs reported are those expected with a hormonal contraceptive.

8.3 LABORATORY TESTING AND VITAL SIGNS

Dr. Popat's review addresses the evaluation of laboratory parameters and vital signs in the phase 3 studies. There were no new safety signals of concern in either area. The pooled phase 2/3 database demonstrated slight alterations in lipids, a known effect of hormonal contraceptives, with a small reduction in HDL and a slightly larger increase in LDL. Shift tables revealed a small, but greater proportion of subjects who shifted from normal to high

for cholesterol, and LDL, compared to the proportion of subjects who shifted from normal to low values. For HDL and triglycerides, the proportion that shifted from normal to low was greater than the proportion that shifted from normal to high. Hematologic parameters did not change markedly during the study. Four subjects with normal baseline values had elevations in liver enzymes, but three of the four resolved, while one was referred for further evaluation. No subject met Hy's law.

There were no notable changes in vital signs or weight over the course of the trial.

8.4 POSTMARKETING SAFETY FINDINGS

Quartette has not been approved for marketing anywhere in the world, so there are no postmarketing safety data on this product. However, safety information has been submitted regularly on the related Seasonale/Seasonique products, and no new safety signals have been observed for this product line.

8.5 SAFETY UPDATE

A 120-day Safety Update was submitted on September 27, 2012, and consisted solely of five updated pregnancy narratives. No new safety findings or concerns were identified by the Applicant.

Team Leader Comment:
I concur that there is no new safety concern based on the Safety Update.

8.6 OVERALL ASSESSMENT OF SAFETY FINDINGS

The clinical safety database for Quartette included more than 4,100 subjects who used the to-be-marketed patch in phase 2 or phase 3, with a total of over 34,000 cycles of exposure in Study 301. There were no deaths. SAEs generally occurred at a rate comparable to that observed in other contraceptive trials. SAEs of concern include suicidal ideation/attempt (two cases), and VTEs, which occurred in multiple subjects in this trial. Although VTE and depression are labeled warnings in contraceptive labels, I recommend that these specific events be described in Quartette labeling. The rate of VTE (3/2,642 women-years) equates to about 11 per 10,000 women-years. Although this is slightly higher than what is described in COC class labeling (3-9/10,000 women-years), it is within the range of VTE incidence noted in large epidemiologic studies [e.g., 8-10 per 10,000 women-years over a variety of different progestins in EURAS], and I do not believe it represents a notably increased VTE risk compared to other EE/LNG products. The total dose of both EE and LNG is similar to that in Seasonale, another 91-day extended cycle COC which does not have a VTE profile of concern.

The suicidality cases are somewhat surprising, but may reflect a population at risk, as it was noted that about half the cases reported a previous psychiatric history. There does not appear to be biological plausibility for a true safety signal, given that the higher dose, but similar dosing regimen product, Seasonique, has not displayed a signal during the postmarketing period.

Discontinuations due to AEs occurred at a rate similar to that in other contraception trials, although there did appear to be a higher incidence of premature termination due to bleeding complaints. Common AE rates were consistent in incidence and type with those expected for a hormonal contraceptive. There were no signals of concern with respect to laboratory

parameters or vital signs. Overall, I believe that the safety profile of Quartette is consistent with that generally observed for other hormonal contraceptives.

9. Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application, as it does not utilize a novel combination of contraceptive hormones or dose regimen, and it is not the first extended cycle COC marketed.

10. Pediatrics

The Applicant requested a waiver of pediatric studies in premenarcheal females (b) (4) because the indication is not relevant to this population. The Applicant also requested a waiver of studies in postmenarcheal females (b) (4), with the justification that safety and efficacy data for this population can be extrapolated from the adult data. The Division concurred that a partial waiver and extrapolation was appropriate. The Pediatric Review Committee (PeRC), on January 9, 2013, agreed to a partial waiver for patients from birth to 11 years of age, and to extrapolate efficacy for patients from 12 to 16 years of age.

11. Other Relevant Regulatory Issues

The Applicant certified that it did not use any debarred investigators. The Applicant submitted financial disclosure information for investigators in Study (b) (6) and only two had any disclosures. Dr. (b) (6) received over $25,000 as a consult to the Applicant regarding its (b) (6) products, and Dr. (b) (6) received $35,000 in speaking and consultant fees from the Applicant, relating to lectures on other contraceptive and hormone therapy products.

The Office of Scientific Investigation (OSI) inspected (b) (6) sites for Study (b) (6). The sites were chosen based on considerations that included the number of subjects enrolled, questions about enrollment/discontinuation status (Dr. (b) (6)), and a possible financial conflict (Dr. (b) (6), who received $35,000 during his participation in the study. Dr. (b) (6) site enrolled only (b) (6) subjects, so inspection of his site was not deemed necessary.

Dr. (b) (6) site (Site (b) (6) screened (b) (6) subjects, enrolled (b) (6) subjects, and (b) (6) completed the study. Records of all (b) (6) subjects were reviewed by OSI. The records for (b) (6) subjects identified by the clinical reviewer as potentially problematic were reviewed in their entirety. (b) (6)

Dr. (b) (6) site (Site (b) (6) enrolling site in the study; it screened (b) (6) subjects, enrolled (b) (6) subjects, and (b) (6) completed the study. Records of (b) (6) subjects were reviewed by OSI. (b) (6) .

Dr. (b) (6) site (Site (b) (6)) screened (b) (6) subjects, enrolled (b) (6) subjects, and (b) (6) completed the study. Records of (b) (6) subjects were reviewed by OSI in full or part. (b) (6)

Roy Blay, Ph.D. from OSI made the following overall assessment and general recommendations in his review dated February 26, 2013:

> *Dr. (b) (6) clinical investigator sites were inspected in support of this NDA. Drs. (b) (6) Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.*

12. Labeling

The Applicant submitted the proposed proprietary name Quartette, which was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and was generally revised in accord with current class labeling for COCs. Input from DMEPA, the Study Endpoints and Labeling Development (SEALD) team and the Office of Prescription Drug Promotion (OPDP) was incorporated in labeling revisions. Agreement on labeling was reached with the Applicant on March 26, 2013.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this NDA receive an Approval action.

13.2 Risk Benefit Assessment

The efficacy of Quartette for prevention of pregnancy is within the range of that for other approved combined hormonal contraceptives. Although the point estimate is the highest approved by the Division, the Applicant conducted a large study and the confidence interval is fairly tight, with an upper bound that is well within the range generally acceptable to the Division. The safety profile does not reveal any new or unexpected safety signals. The overall risk/benefit profile is acceptable.

13.3 Recommendation for Postmarketing Risk Management Activities

None

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

None

13.5 Recommended Comments to Applicant

None

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

/s/

LISA M SOULE
03/27/2013

AUDREY L GASSMAN
03/27/2013
I concur with the recommendations in this review