CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204061
Priority or Standard	Standard
Received Date(s)	May 31, 2012
PDUFA Goal Date	March 31, 2013
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Vaishali Popat, MD, MPH
Review Completion Date	February 28, 2013
Established Name	levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets
(Proposed) Trade Name	Quartette
Therapeutic Class	Combination oral contraceptive (COC)
Applicant	Teva Branded Pharmaceutical Products R&D, Inc.
Formulation(s)	Days 1 through 42: LNG 150 mcg/EE 20 mcg Days 43 through 63: LNG 150 mcg/EE 25 mcg Days 64 through 84: LNG 150 mcg/EE 30 mcg Days 85 through 91: EE 10 mcg
Dosing Regimen	One tablet daily
Indication(s)	Prevention of pregnancy
Intended Population(s)	Women of reproductive age at risk for pregnancy who desire contraception

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for the primary indication of contraception. There are no new and unexpected safety issues identified upon review of the safety database submitted in this NDA or any suggestion that use of this product will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs. There were 3 deep venous thromboses (DVT) in the pivotal trial 301. The occurrence of 3 thromboembolic events in comparable size trials is not uncommon.

The contraceptive benefit of this product is comparable to that of other approved COCs.

Table 1 presents the key contraceptive efficacy results based on 70 "on-drug" pregnancies. This reviewer identified five additional pregnancy not considered "on-drug" by the Applicant (the originally provided Pearl Index calculations were based on 65 pregnancies).

Table 1: Summary of Pearl Index analyses for complete 28-day cycle-equivalent – PITT population

	N	Number of on-drug Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
Applicant	2992	67	30,363	1848	28,515	3.05	(2.37, 3.88)
Reviewer	2992	70	30,363	1848	28,515	3.19	(2.49, 4.03)

Site LA0012 is excluded. CI= Confidence Interval
Source: Statistical reviewer (Dr. Guo) 's analysis

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Standard post-marketing surveillance is recommended to further monitor the safety of Quartette. No specific risk management steps are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no required phase 4 requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Quartette is a 91-day extended cycle oral contraceptive (OC) with ascending doses of EE as described below. The combination product contains levonorgestrel (LNG) and ethinyl estradiol (EE); an ethinyl estradiol tablet is also included for the final 10 days of the extended cycle. This product is similar to other approved extended cycle COCs as shown in Table 2; the total LNG dose over the extended cycle is the same as that in Seasonale and Seasonique, while the total EE dose is bracketed by Seasonale/Seasonique and LoSeasonique.

Table 2: Comparison of 4 similar products (differences are bolded)

Products	Dosage Regimen
Proposed Product (Quartette or DR-103)	Days 1 through 42: LNG 150 mcg/EE 20 mcg Days 43 through 63: LNG 150 mcg/EE 25 mcg Days 64 through 84: LNG 150 mcg/EE 30 mcg Days 85 through 91: EE 10 mcg
Seasonale	Days 1 through 84: LNG 150 mcg/EE 30 mcg Days 85 through 91: **Placebo**
Seasonique	Days 1 through 42: LNG 150 mcg/EE 30 mcg Days 85 through 91: EE 10 mcg
LoSeasonique	Days 1 through 84: LNG **100** mcg/EE 20 mcg Days 85 through 91: EE 10 mcg

2.2 Tables of Currently Available Treatments for Proposed Indications

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs, Progestin-only oral contraceptives
- Intrauterine devices (LNG-containing and copper-containing)
- Injectable contraceptives, Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

Combination 28-day OC products containing LNG and EE have been marketed for decades worldwide. When OCs were first introduced, the dosage regimen was designed to induce withdrawal bleeding every 28 days.

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

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

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

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

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

Quartette is a somewhat unique OC because it combines an ascending dose LNG/EE regimen with the EE 10 mcg monotherapy given during Days 85-91 of the cycle as follows:

- 42 days combination therapy of 20 mcg EE/150 mcg LNG followed by
- 21 days combination therapy of 25 mcg EE/150 mcg LNG followed by
- 21 days combination therapy of 30 mcg EE/150 mcg LNG followed by
- 7 days of 10 mcg EE

The Applicant’s rationale for the proposed regimen is that the gradual increase in EE dose may provide better protection against unscheduled (“breakthrough”) bleeding or spotting than the sustained lower concentrations of EE in LoSeasonique. Furthermore, the Applicant believes that the stepwise increase may be better suited to preventing these effects as compared to the persistent higher concentrations of EE in Seasonique, which may desensitize the estrogen receptors. The clinical trial data did not show any particular advantage over other COCs.

2.3 Availability of Proposed Active Ingredient in the United States

Ethinyl estradiol is the most commonly used estrogen in combination oral contraceptives, with nearly 50 years of marketing experience.

Levonorgestrel has been studied since the early 1950s and has been marketed in COCs since the 1960s.

2.4 Important Safety Issues with Consideration to Related Drugs

COCs as a general class have a number of safety issues that have been well-recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may be fatal, including:
  - Deep venous thrombosis, pulmonary embolism, other venous thromboses
  - Myocardial infarction (especially in women >35 years who smoke)
  - Stroke (both ischemic and hemorrhagic types reported)
- Hepatic adenomas, hepatic nodular hyperplasia, cholestasis
- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea
- Breast tenderness
- Mood changes
- Hypertriglyceridemia

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 72,290 was opened on 5/31/2006. A PIND Type B Teleconference post held on August 7, 2006. Important points discussed at this meeting were a Division recommendation to remove restrictions based on BMI, due to the importance of having adequate clinical data on overweight subjects.

A pre-NDA meeting was scheduled for June 23, 2009 but withdrawn when the Applicant received the DRUP written responses to their questions. Pertinent clinical comments expressed by the Division are the following:

- The primary efficacy analysis should be based on the PITT population (all women ages 18-35 who completed at least one 28-day cycle of therapy) and exclude all 28-day cycles where any other birth control method (including condoms and emergency contraception) was used, unless a pregnancy occurred in such a cycle.
- The 28-day cycle Pearl Index calculation should be revised to

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

  In the additional evaluation of pregnancy rates calculated by the life table method, provide data based on 28-day cycles as well as by 91-day cycles.
- Specify how pregnancies will be dated (e.g., based on last menstrual period, first trimester ultrasound, etc.).

Medical Officer's Comment:

- ***Overall, this Applicant has experience in developing COCs such as NDA 21-544 (Seasonale), NDA 21-840 (Seasonique), NDA 22-262 (LoSeasonique). Therefore, the Applicant did not require extensive guidance in development of this product, Quartette.***
- ***Even though this was a 91-day cycle regimen, the Division typically evaluates primary efficacy endpoint, PI, according to 28-day cycles. This approach retains more data as if another birth control method is used in a cycle, only 28 days of data, rather than 91 days, need to be excluded as unevaluable.***

2.6 Other Relevant Background Information

Relevant INDs, NDAs, BLAs and DMFs: IND 072290, NDA 21-544 (Seasonale), NDA 21-840 (Seasonique), NDA 22-262 (LoSeasonique), DMF (b) (4) for LNG and DMF (b) (4) for EE.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant provided statements in their pivotal phase 3 Trial 301 and phase 2 Study DR-ASC-201 that the study met all local legal and regulatory requirements. Protocols and protocol amendments were reviewed and approved by each of the study sites' Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

The FDA's Office of Scientific Investigations (OSI) investigated 3 clinical sites at the request of DRUP (Table 3). These sites were chosen primarily based on the number of subjects (Site 034, N=184), incorrect coding of the subjects (Site 079: Lost to follow-up pregnancy, miscoded disposition and relatively large number of subjects enrolled, N=62), an investigator with financial conflict of interest (Site 071) and lack of recent inspections. The data from these sites was deemed acceptable by OSI with no evidence of discrepancies or regulatory violations.

Table 3: Site selection for inspection

Site # (Name, Address, Phone number)	Study #	Number of Subjects	Indication
Site # 079 William Seger Benchmark Research 4504 Boat Club Road, Suite 400A Fort Worth, TX 76135 817.238.7254	DR-103-301	62	Prevention of Pregnancy
Site # 034 Janet Gersten New Age Medical Research Corporation 8900 Southwest 117th Avenue Suite 207-B Miami, FL 33186 305.596.9901	DR-103-301	184	Prevention of Pregnancy
Site # 071 David Portman Columbus Center for Women's Health Research 99 N. Brice Road, Suite 120 Columbus, OH 43213 614.861.6707	DR-103-301	78	Prevention of Pregnancy

At the time of initial evaluation of the site selection, Site LA0012 was chosen primarily because it had a large number of subjects withdrawn due to the Applicant request. When the OSI inspector contacted the Applicant to arrange for the site inspection, the Agency was notified of the termination of Site LA0012 (Investigator (b) (6) , MD) from study participation. The Applicant acknowledged in the response to information request dated 9/21/2012 that the termination letter for this site was inadvertently not submitted with the New Drug Application (NDA). The Applicant also noted that in responding to the Division's questions, it was discovered that the data and analyses provided in the original NDA erroneously included the data from Site LA0012 despite a prior decision by the Applicant to exclude these data.

At the time Site LA0012 was terminated from study participation, none of the 34 subjects enrolled at this site had completed the study. A total of 14 subjects were discontinued from the study due to site termination; the remaining 20 subjects had discontinued study participation due to adverse events (10 subjects), subject request (2 subjects), or loss to follow-up (8 subjects). Subjects who were discontinued due to the Applicant's termination of Site LA0012 had completed 2-4 ninety-one–day cycles of exposure to the investigational product (6-13 twenty-eight–day cycles) at the time of their discontinuation.

Impact of site termination on the efficacy data is as follows:

No pregnancies were reported at Site LA0012, and a total of 155 treatment cycles were excluded from the Pearl Index calculations as a result of removing the data from this

site from the analysis. Analysis of PI including or excluding this site did not make any major difference in conclusion of the efficacy. In this review, PI calculations are presented in section 6 excluding this site.

Medical Officer's Comment:
Excluding or including data from this site did not have a major impact in the final conclusions.

3.2 Compliance with Good Clinical Practices

The Applicant provided statements in all of their clinical trials (study protocols for Trial 301 and 201) that the studies were conducted in accordance with Good Clinical Practice (GCP). The Applicant certified that the services of any person debarred under section 306(a) and (b) were not used in any capacity in the clinical trials.

The Applicant reported the details of the 9 site audits as follows:
Eight out of 9 audited sites in Study 301 were found to be in compliance with GCP. Site LA0012 was discontinued and reasons for termination included the following audit findings:

- Intentional backdating of laboratory results and adverse event assessments by Dr. (b) (6)
- Obtaining and transporting laboratory samples in a manner that did not ensure the integrity of the blood samples
- Complete lack of oversight, involvement, supervision, and proper delegation to staff by Dr. (b) (6)

3.3 Financial Disclosures

There were a total of 98 centers in the USA for Trial 301 and 51 centers in the USA for Trial 201 in the submission. Of these, for Trial 301, there were 2 investigators with disclosable financial information (Dr. (b) (6) and Dr. (b) (6)). Dr. (b) (6) received $35,000 in speaking and consulting fees from Teva Women's Health in 2010. These fees were for lectures on (b) (6), not drugs directly involved in this product's development. Due to this potential conflict of interest and high number of subjects enrolled (b) (6), a DSI inspection was requested for his site. Another investigator, Dr. (b) (6) (Site (b) (6)), also reported >$25,000 in payments from Teva. We analyzed efficacy data excluding these sites, which showed no significant difference in the results. The PI excluding the two sites for 28-days is 3.15 (95% CI: 2.45 - 3.99). The PI for 91-day is 3.48 (95% CI: 2.70 - 4.40). By excluding these two sites, three on-drug pregnancies were removed from the Pearl Index calculation. Including the two sites, the 28-day PI is 3.19 (95% CI 2.49- 4.02), the 91-day PI is 3.52 (95% CI: 2.75-4.43).

Reviewer's comment:

Although there were investigators with financial disclosures, based on the assessment so far, it is unlikely that their contributions affected the outcome of the studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drug name: Quartette (received conditional approval from the Division of Medication Error Prevention and Analysis).

Established Name: levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets

Chemical Name: 18,19-Dinopregn-4-en-20yn-3-one, 13-ethyl-17-hydroxy-,(17α)-,(-)- for levonorgestrel and 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)- for ethinyl estradiol

Molecular Formula/Molecular Weight: $C_{21}H_{28}O_2$/312.5 for levonorgestrel

$C_{20}H_{24}O_2$/296.4 for ethinyl estradiol

Drug Substance:
The two drug substances are levonorgestrel and ethinyl estradiol. The Applicant references DMF (b) (4) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of levonorgestrel. A Letter of Authorization is provided in the application. The Applicant cross references DMF (b) (4) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of ethinyl estradiol. A Letter of Authorization is provided in the application.

Table 4: Ingredients in Quartette

Ingredients for LNG/EE tablets	Ingredients for EE tablets
(b) (4) LNG, USP (b) (4) EE, USP anhydrous lactose, NF hypromellose (b) (4), USP (b) (4) cellulose, NF magnesium stearate, NF and (b) (4)	(b) (4) EE, USP anhydrous lactose, NF polacrilin potassium, NF (b) (4) cellulose, NF magnesium stearate, NF and (b) (4) yellow

Medical Officer's Comment:
Excipients used in both LNG and EE tablets are not novel and are the same as the excipients used in the manufacturing of Seasonique tablets.

Drug Product:
The blister film used for packaging Quartette is a (b) (4) film that combines (b) (4) The push-through blister foil is (b) (4) aluminum foil that is printed on both sides. Sealed pouches are then placed in a cardboard carton. The drug product is manufactured by Teva Laboratories. Based on the stability data, an 18-month expiration dating period, as requested by the applicant, has been granted for storage at 25°C/60% relative humidity (controlled room temperature).

Medical Officer's Comment:
There are no major issues from the CMC perspective, according to the CMC reviewer, Dr. Agarwal. In his review, he noted the following:

- ***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.***

4.2 Clinical Microbiology

Microbiology review was not needed for this application because the product consists of oral tablets.

4.3 Preclinical Pharmacology/Toxicology

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

Medical Officer's Comments

- ***In December 28, 2011 correspondence, the Applicant stated that Teva Women's Health has not conducted a nonclinical program for Quartette, as LNG and EE alone or in combination, are well-studied and have a well-known pharmacology/toxicology profile. Based on this information Applicant stated that they intend to reference the nonclinical pharmacology/toxicology information contained in submissions from their previously approved LNG/EE oral contraceptive products under NDAs 21-544, 21-840 and 22-262 for Seasonale, Seasonique and LoSeasonique, respectively. The Agency agreed with the Applicant's request not to conduct any more nonclinical toxicology studies.***

- ***The Pharmacology Toxicology (P/T) reviewer, Dr. Raheja states following in his review: P/T recommends approved of NDA 204061 for prevention of pregnancy.***

4.4 Clinical Pharmacology

Mechanism of Action

Quartette lowers the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

Absorption

Levonorgestrel is completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is absorbed from the gastrointestinal tract but, due to first-pass metabolism in the gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 40%. Maximum plasma concentrations occur within 2 hours after oral administration.

Systemic exposure to ethinyl estradiol following administration of Quartette increases linearly in an approximate dose-proportional manner over the range of doses within this product. Systemic exposure to EE (as assessed by AUC) at steady state following administration of Quartette is approximately 20% higher than expected based on single-dose data. This may be due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Food Effect

The effect of food on the rate and the extent of levonorgestrel and ethinyl estradiol absorption following oral administration of Quartette has not been evaluated. The phase 3 study dosing was done without regard to meals and based on experience with the drugs containing LNG/EE, there is no concern related to impact of a food effect.

Renal or Hepatic Impairment

The pharmacokinetics of Quartette tablets have not been studied in subjects with renal impairment. No studies have been conducted to evaluate the effect of hepatic disease on the disposition of Quartette. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

Overall Assessment

The primary Clinical Pharmacology Reviewer, Sayed Al Habet, PhD stated the following in his review: ‘The NDA can be filed from the clinical pharmacology perspective.’

Dr. Al Habet did not request any Phase 4 commitments.

5 Sources of Clinical Data

The Clinical study reports, data, and additional information were submitted electronically.

Tables of Studies/Clinical Trials:

The two clinical studies (one phase 2 and one phase 3 clinical trial) with most pertinent clinical data are presented in Table 5.

Table 5: Table of clinical trials

Study Phase	Dates	Study population Variables	Dose regimen Duration of treatment	Number treated
DR-ASC-201 **Phase 2** **51 US centers**	27 Oct 06 to 04 Mar 08	Healthy women Primary efficacy endpoint: total bleeding and/or spotting days during active treatment	Eligible subjects receive a 28-day run-in cycle of Portia taken orally (21 days of 30 mcg EE/150 mcg LNG followed by 7 days of placebo) Subjects were randomly assigned to 1 of the following for 2 consecutive 91-day extended cycles): Group 1 (low dose) Group 2 (midrange dose) Group 3 (high dose) Group 4 (Seasonale) Total duration: ~ 9 months	N=567 (safety) Age 30.5 Weight: 154.4 lb.
DR 103-301 **Phase 3** **98 US centers**	08 Oct 09 to 09 Sep 11	Healthy, sexually active women who were at risk of pregnancy Primary efficacy endpoint: Pearl Index using all pregnancies Secondary efficacy endpoint: life table analysis using cumulative pregnancy rates	LNG/EE tablets OC regimen 42 days:20 mcg EE/150 mcg LNG, 21 days:25 mcg EE/150 mcg LNG, 21 days:30 mcg EE/150 mcg LNG, followed by 7 days of 10 mcg EE Total duration: 1 year	N=3597 Age: 27.1 Weight: 162.5 lb

Source: Tabular listing of all clinical studies.

5.2 Review Strategy

Sections 5.3.1 and 5.3.2 contain detailed information about the pivotal contraceptive safety and efficacy study and the supportive phase 2 study.

- Trial DR-103-301 is referred as Trial 301 in this review.
- Trial DR- ASC -201 is referred as Trial 201 in this review.
- Quartette is used interchangeably with 'Low dose' in this review.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 301

5.3.1.1Study Title / Study Dates

"A multi-center, open-label study to evaluate the efficacy and safety of a combination oral contraceptive regimen for the prevention of pregnancy in women"

Original Protocol Final Issue Date: 22 July 2009
Amendment 1 Final Issue Date: 10 May 2010

The study ran from 08 October 2009 to 09 September 2011.

5.3.1.2 Ethics

The Applicant stated that:

- The protocol, protocol amendments, and informed consent documents were reviewed and approved by an Investigational Review Board (IRB) in accordance with the provisions of 21 CFR Part 56.
- The study was carried out in accordance with Good Clinical Practice (GCP) and the United States (US) Code of Federal Regulations, Title 21. These standards respect the following guidelines: International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, the Guideline for Good Clinical Practice, and the Declaration of Helsinki and amendments.

5.3.1.3 Study Sites

In Trial 301, 98 study sites screened and randomized subjects. All sites were in the USA.

5.3.1.4 Study Objectives

The primary objective of this study was to demonstrate the efficacy and safety of a 91-day combination OC regimen (Quartette), utilizing ascending EE doses during the 84-day cycle of EE/LNG followed by 7 days of EE; this regimen was followed for 1 year in women desiring pregnancy prevention.

No secondary objectives were defined in the protocol.

5.3.1.5 Study Design

Trial 301 was designed as a phase 3, multicenter, open-label, uncontrolled clinical trial. The trial was designed to run for 4 cycles (91 days per cycle). The drug dosages changed in a phasic manner in each cycle, as shown below:

- 42 days combination therapy of 20 mcg EE/150 mcg LNG followed by
- 21 days combination therapy of 25 mcg EE/150 mcg LNG followed by
- 21 days combination therapy of 30 mcg EE/150 mcg LNG followed by
- 7 days of 10 mcg EE

This dose regimen was chosen based on the bleeding profile of the three regimens evaluated in the phase 2 dose-finding study.

The study consisted of a Screening Period (4 weeks), a Treatment Period (12 months), and a Post-Treatment Period (3 weeks).

The study plan called for 3,600 heterosexually active women aged 18 to 40 and at risk of becoming pregnant to be enrolled to achieve a minimum of approximately 20,000 twenty-eight-day cycle-equivalents and 1,670 subjects completing the planned 1-year duration of treatment. The pregnancy rate was to be assessed in terms of the Pearl Index and by life table methods.

All pregnancies occurring during the study and within 30 days after the end of treatment were assessed to determine their relationship to the use of study drug. Pregnancies found to have an estimated date of conception within 7 days after the last study treatment (whether this was a combination tablet or an EE-alone tablet) were to be counted as “on-drug” pregnancies.

All subjects were to complete a daily diary to record IP use, occurrence/severity of bleeding or spotting (B/S), the use of condoms or other contraceptive methods, and the use of concomitant medications.

All subjects were to be “Sunday starters” and remain “Sunday starters” throughout the duration of the study.

- New Starts or Prior Users who are not currently using a hormonal contraceptive were to initiate IP on the first Sunday following the first day of bleeding for the menses that is concurrent with or follows the Enrollment Visit.
- Continuous Users who are currently Sunday Starters were instructed to complete their current cycle of therapy and initiate IP on the Sunday they would normally have begun their next cycle of OCs. Continuous users on an extended cycle OC did not have to complete an entire 91-day extended cycle. Subjects could stop at the end of 28 days or 56 days and then start IP.

- Continuous Users who were not Sunday Starters were to initiate IP on the first Sunday following the last day of active hormonal administration from their prior contraceptive regimen.

Medical Officer's Comment:
The proposed labeling describes only a Sunday Start, which is consistent with the clinical trials practice.

Subjects could have been withdrawn from the study at the discretion of the investigator or Applicant due to poor compliance with protocol requirements or IP use.

Subjects agreed to routinely use the study OC as their only birth control method (BCM). However, subjects were instructed that another non-hormonal BCM (such as condom, spermicides, or contraceptive sponge) must be used as a back up for the first 7 days of IP use and in situations where 2 or more pills in a row were missed.

5.3.1.6 Key Inclusion Criteria

1. Sexually active females who are at risk for pregnancy
2. Age 18 through 40 years at the time of the Screening Visit
3. Able to complete all study procedures, including the required diaries and all study visits
4. Agree to routinely use study OC as their only BCM during the study. When intermittent therapies with drugs known to interact with OCs were initiated, another non-hormonal BCM was to be used for the entire time the subject received the therapy and for a minimum of 7 days following discontinuation of the medication
5. For all subjects not currently using extended cycle contraception, subjects must have a history of regular (approximately monthly) spontaneous menstrual cycles, or withdrawal bleeding episodes, for the 3-month period preceding the Screening Visit. For subjects using extended cycle contraception, subjects must have completed a minimum of 1 extended cycle, including a withdrawal bleed prior to beginning the extended cycle and a withdrawal bleed at the completion of the cycle prior to the Screening Visit.

5.3.1.7 Key Exclusion Criteria

1. Any condition (history or presence of) which contraindicates the use of combination OCs, including: thromboembolic disorders, cerebrovascular or coronary artery disease or myocardial infarction, diabetes mellitus, migraine headaches with focal, neurological symptoms; chronic renal disease; uncontrolled or untreated hypertension (BP ≥ 140/90 mmHg), cholestatic

jaundice; estrogen-dependent neoplasia; undiagnosed abnormal genital bleeding (within 180 days); Impaired liver function, hepatic adenomas or carcinomas;

2. Breastfeeding
3. History of alcohol abuse, illegal drug user; use of drugs that, as stated in the product labeling, require simultaneous use of contraceptives (e.g., isotretinoin [Accutane])
4. History of being Human Immunodeficiency Virus (HIV) or Hepatitis C positive
5. History of having received injectable hormone therapy (e.g. Depo-Provera) within the 6 months prior to the Screening Visit or having a progestin-releasing intrauterine device (IUD) in place within 1 month prior to the Screening Visit or had a contraceptive implant removed within 1 month prior to the Screening Visit; use of non-contraceptive sex hormonal therapy, administered by any route, within 3 months prior to the Screening Visit
6. Routine, concomitant use of additional forms of contraception (diaphragm, spermicides, contraceptive sponge, condoms) except as specified in the protocol. A subject who routinely requires use of a condom for protection from sexually transmitted diseases (STDs)
7. Hyperlipidemia on Screening (fasting cholesterol level >260 mg/dl; fasting triglyceride level >300 mg/dl)
8. Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap smear. Any other abnormal finding on the Pap smear that the investigator considers clinically significant. Investigator's decision was documented
9. Has participated in any clinical investigation utilizing an investigational drug or medical device or requiring invasive gynecological procedures within the 30 days prior to the Screening Visit.

5.3.1.8 Study Procedures

Clinic visits occurred approximately monthly during Cycle 1, twice during Cycle 2, and once each during Cycles 3 and 4 (Visits 2-8). Visits could be conducted earlier than specified in the protocol with approval from the Applicant. Visits conducted later than specified in the protocol that result in a lapse in use of study drug were documented as a protocol violation and may have resulted in the subject being withdrawn from the study. At Visit 0, subjects who were continuous users but did not want to continue their current method for any reason but remained eligible were offered Portia as a bridge while completing Screening assessments until they were able to start IP.

Subjects were contacted by telephone:

- approximately 3 days following the anticipated IP start date to confirm onset of the subject's menses, commencement of IP, and date of last use of the active hormonal component of their previous birth control method, if applicable

- during Weeks 17, 23, 30, 34, 43, and 47 between scheduled clinic visits to query/record AEs, ensure subject compliance with IP/diary recording, and confirm negative home UPT
- during Week 53 (Week 52 + 1 week) to document post-treatment birth control method and start date.

Table 6: Study 301 Schedule of assessments

Parameter	Visit 0 Screening	Visit 1 Enroll	Visits 2-7	Visit 8/ Early Withdrawal	Telephone FU	Visit 9 Final Visit
Weeks from First Dose of Investigational Product	-4	0	4, 8, 13, 19, 26, 39	52	1, 17, 23, 30, 34, 43, 47, 53	52 + 3 Weeks
Informed Consent	X					
Inclusion/Exclusion Criteria Review	X	X				
Medical/Gynecologic/Contraceptive History	X					
Physical and Gynecological Exam	X			X		
Pap Smear	X			X		
Height	X					
Weight, Vital Signs	X	X	X	X		X
Clinical Laboratory Tests	X			X		
Serum Pregnancy Test	X					
Urine Pregnancy Test	X	X	X	X	X	X
Record Historical or Concomitant Medications & Smoking Habits or Changes in Smoking Habits	X	X	X	X		X
Distribute & Collect IP		X	X	X		X
Distribute & Collect Portia				X		X
Distribute Subject Diary including Instruction		X				
IP Compliance & Reinstruction as necessary			X	X	X	X
Collect/Review Subject Diary & Reinstruct, as necessary			X	X	X	X
Adverse Event Recording		X	X	X	X	X

Source: Page 36 of the protocol-am-01-study-301

The Final Study Visit occurred approximately 21 days (acceptable window was 21-28 days) following the last dose of IP for all subjects, including those who completed the study and those who were withdrawn or discontinued the study early for any reason. The subject was asked to return all study supplies (IP and diary) at this visit.

The IP and a Subject Information Sheet were given to subjects at Visits 1-7. At Visit 7, subjects were counseled on contraceptive options following their last dose of IP. At Visit 8/Early Withdrawal, subjects were offered a 28-day pack of Portia (provided to sites by the Applicant) with a copy of the Portia Subject Information Sheet.

Visit 9 was required for all subjects who took one or more doses of IP. However, Visit 9 did not need to be completed for subjects who had IP dispensed but never took it.

Medical Officer's Comments:
The trial design is consistent with other approved contraceptive trial designs.

Subject Diary
Subjects completed a paper diary on a daily basis beginning with the first day of IP and continuing through the last dose of IP. IP use, occurrence/severity of bleeding or spotting (B/S), the use of condoms or other contraceptive methods, and the use of concomitant medications were recorded.

Compliance with IP use was assessed by pill counts at scheduled study visits and subject daily diary completion. Subjects were to bring their pill pack(s) with them to each study visit and return all remaining pill packs at the Final Study Visit or Early Withdrawal Visit. A photocopy of all returned pill packs was added to the permanent study record for each subject.

Withdrawal of Subjects
Any subject who withdrew from the study prematurely was required to return the IP (all used and unused pill packs), and the subject daily diary, and was requested to complete all the procedures described for the Visit 8/Early Withdrawal Visit and Visit 9/Final Study Visit. The reason(s) the subject was withdrawn or requested withdrawal from the study was specified on the electronic case report form (eCRF) along with the date of study withdrawal and the date of discontinuation of IP.

Subjects could be withdrawn from the study at any time for any reason. Possible reasons for termination included the following:

- Any condition or abnormal laboratory finding, which in the opinion of the investigator or the Applicant contraindicates the continued use of OCs
- Subject requests withdrawal from the study
- An AE that makes subject continuation impossible or inadvisable
- Pregnancy
- Discovery that an enrolled subject did not meet or does not continue to meet the protocol entrance criteria
- Subject requires chronic therapy with a prohibited medication
- Subject non-compliant or lost to follow-up
- Subject non-compliant with diary completion and/or IP use

- Involvement in a study using any additional experimental drug or device or requiring invasive gynecological procedures
- Applicant termination of the study or site

If a subject was lost to follow-up, the early withdrawal date was defined as the date of last contact.

5.3.1.9 Primary Efficacy Variable

The primary efficacy analysis was based on the Pearl Index in the group of women 18-35 years of age based on all at-risk cycles; i.e., those in which no other method of birth control was used. The 95% CIs for the Pearl Indices and life table estimates were also computed.

The Pearl Index is a derived variable and the algorithm for derivation is given below. Pregnancies considered 'On-drug' by the Applicant had to satisfy the following criteria:

- Pregnancy is defined as a positive pregnancy test
- Pearl Index calculation includes all pregnancies conceived from IP start date to 7 days after intake of the last tablet.
- Each subject's treatment duration was broken down into 28-day cycles starting from their first dose date.

5.3.1.10 Secondary Variables

Cumulative pregnancy rates at the end of the treatment period (following completion of four 91-day cycles) were determined using the life table method. Time intervals were based on cycle duration; i.e., 91 days. The 95% confidence intervals were presented for the life table estimates of cycle-specific pregnancy rate.

The secondary variables were the descriptive parameters of bleeding/spotting. Total number of days of bleeding and/or spotting (withdrawal menses [scheduled bleeding] and unscheduled bleeding) reported by study subjects in the daily diary were to be summarized using descriptive statistics for each 91-day cycle. The results of these analyses will be presented in the safety section. The definitions for bleeding patterns are presented here.

<u>Bleeding/Spotting</u>
The following definitions were employed to analyze bleeding/spotting in Study 103.

Table 7: Definitions employed to analyze bleeding/spotting

Term	Definition
Bleeding/Spotting score = 0	No vaginal bleeding
Bleeding/Spotting score = 1	**Spotting**= requiring less than one pad or tampon per day
Bleeding/Spotting score = 2	**Light** = 1-2 pads or tampons per day
Bleeding/Spotting score = 3	**Moderate** = 3-5 pads or tampons per day
Bleeding/Spotting score = 4	**Heavy** = 6+ pads or tampons per day

A sample from the subject diary is represented below:

Week Starting on Sunday TO Week Ending on Saturday	Place an 'X' in the box each day you take your pill.	Record Bleeding or Spotting for each day of the week. Spotting= < 1 pad/tampon/day Moderate = 3-5 pads/tampons/day Light = 1-2 pads/tampons/day Heavy = 6+ pads/tampons/day	Did you use a condom this week?	Did you use another form of contraception "*other than condom*", this week?
d d m m m 20 y y TO d d m m m 20 y y	SUN (1) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy	(1) ☐ Yes (0) ☐ No	(1) ☐ Yes (0) ☐ No
	MON (2) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		
	TUE (3) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		
	WED (4) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		
	THUR (5) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		
	FRI (6) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		
	SAT (7) ☐	(0) ☐ None (1) ☐ Spotting (2) ☐ Light (3) ☐ Moderate (4) ☐ Heavy		

Source: sample CRF

Medical Officer's Comment:
As subjects were required to follow a Sunday-start regimen, they might still have been experiencing their prior menses when initiating Quartette. This bleeding would have been recorded in their diary, and, as subjects were taking their combination tablets, would have been categorized as unscheduled bleeding. This may artificially inflate the prevalence of "unscheduled" in the first cycle.

The following parameters of bleeding were calculated for each study subject, by cycle and overall:

- Total number of bleeding and/or spotting days reported for each 91-day treatment cycle
- Number of "unscheduled" bleeding and/or spotting days (defined as bleeding during the 84 days of combination therapy)
- Number of "scheduled" (i.e., "withdrawal") bleeding and/or spotting days reported (defined as bleeding and/or spotting during the 7-day EE 10 mcg monotherapy interval on Days 84-91).

5.3.1.11 Statistical Analysis Plan

Population definitions:
Safety Cohort: All subjects who received at least 1 dose of IP were included in the safety cohort evaluated for safety (i.e., Adverse Events (AEs), vital signs, and laboratory results). Subjects for whom pill intake could not be verified were included, with the assumption that they took at least 1 dose.

Intent-to-Treat Cohort (ITT): All enrolled subjects who completed at least one 28-day cycle of IP (a partial cycle in which a subject became pregnant was considered a complete 28-day cycle) were included in the ITT cohort. The ITT cohort was used for all endpoints other than pregnancy.

- Treatment compliance: per the SAP, treatment compliance was to be derived as the percentage of pills taken of the total dispensed at the start of each 91-day cycle. In order to be consistent with the other OC studies, treatment compliance was derived using the total number of pills taken according to the drug accountability logs in the eCRFs divided by the exposure to IP in days, times 100.
- Per guidance received on March 29, 2012 from the Division, bleeding analyses were evaluated after stratification by weight (90 kg and ≥ 90 kg), BMI (< 30 kg/mg^2 and ≥ 30 kg/mg^2), age (< 30 years and ≥ 30 years), smoking (yes and no), and race (Caucasian and other). No formal statistical comparisons were made between these subgroups.

Imputation
No specific procedure was used to impute missing data. Only subjects who had actual recorded data for a particular endpoint at the time of interest were included in the evaluation of the endpoint. Bleeding data from incomplete cycles were not included in the original analysis.

5.3.1.12 Analysis of Safety

The safety monitoring employed in this protocol included medical history, physical exams, vital signs monitoring, safety labs, pap smears, bleeding pattern assessment and adverse event (AE) reporting. The MedDRA coding dictionary was used to assign preferred terms to adverse events.

Laboratory data were collected at the screening visit (Visit 0) and at Week 52 (Visit 8).

5.3.1.13 Protocol Amendments

There was one protocol amendment that included a change of the Final Study Visit from approximately 31 days following the last dose of IP to approximately 21 days. Other changes in the amendment were clarifying or administrative.

5.3.1.14 Disposition of Subjects

Disposition is reported separately for both trials as duration of these trials were different. Trial 301 was of 12 months duration and Trial 201 was for 6 months duration. Disposition for Trial 301 is presented in Section 6.1., with the main efficacy results.

5.3.1.15 Protocol Deviations

Reports from site clinical study staff or data captured on the eCRF and subject diary were used to determine if a subject had deviated from or violated the protocol.

- Six hundred and one subjects (17.9%) in the ITT population took at least one dose of prohibited medications. Only 13 (0.4%) of these subjects had violations that were considered severe enough to necessitate discontinuation by the investigator.

- Eighteen subjects (0.5%) in the ITT population had < 80% overall compliance to IP.

In addition to prohibited medication use or IP noncompliance of less than 80% (i.e., "overall compliance"), other protocol deviations reported for Study 301 included the following: procedure not done according to the protocol (e.g., urine pregnancy test, physical/gynecologic examination, Pap smear not performed for subjects who withdrew from the study shortly after enrollment); out-of-window visits/telephone contacts; diary not completed accurately or pages lost; inappropriate IP use (e.g., missed taking IP, used pill pack not returned, procedure for missed IP not followed, first IP dose not started on first Sunday after start of menses, first dose taken more than 7 days after start of menses, non-hormonal back-up contraception not used during first week of IP use).

Medical Officer's Comments:
The Applicant did not initially provide overall information on protocol deviations for those who remained in the study. They provided this information after the Division's request, in the Aug 3, 2012 submission. These deviations were reviewed and not found to be significant in terms of the efficacy analysis. Because there is only one pivotal clinical trial (301), results of the efficacy analysis are presented in section 6 and safety analyses are presented in Section 7.

5.3.2 Trial DR-ASC-201 (201)

5.3.2.1 Study Title

A prospective, multicenter, double-blinded, randomized study to evaluate bleeding patterns in women using one of three different ascending EE dose extended cycle (91-day) oral contraceptive regimens (Quartette) compared to Seasonale oral contraceptive regimen.

5.3.2.2 Study Dates:

First subject enrolled: *27 October 2006*
Last subject completed: *4 March 2008*

5.3.2.3 Study Sites:

53 United States **(**US) centers

5.3.2.4 Study Objectives:

The Applicant evaluated three different treatment schedules with DR-103 to evaluate and compare bleeding patterns with the monophasic Seasonale 91-day oral contraceptive regimen in order to determine the ascending EE dose regimen(s) to be further evaluated in phase 3.

5.3.2.5 Study Design

All four treatment regimens consist of combination active tablets containing EE and 150 mcg LNG as described below in Table 8.

After one run-in cycle of Portia (LNG/EE oral tablets 150 mcg/30 mcg followed by 7 days of placebo), subjects were randomized to the following treatment groups for two 91-day cycles.

Table 8: Dosing scheme for Trial 201

Group	Dosing x 2 (Two 91-day cycles)
1 "Low dose"	42 days - LNG/EE Tablets 150 mcg/20mcg 21 days - LNG/EE Tablets 150 mcg/25mcg 21 days - LNG/EE Tablets 150 mcg/30mcg 7 days - EE Tablets 10 mcg
2 "Mid-range dose"	21 days - LNG/EE Tablets 150 mcg/20mcg 42 days - LNG/EE Tablets 150 mcg/25mcg 21 days - LNG/EE Tablets 150 mcg/30mcg 7 days - EE Tablets 10 mcg
3 "High dose"	21 days - LNG/EE Tablets 150 mcg/20mcg 21 days - LNG/EE Tablets 150 mcg/25mcg 42 days - LNG/EE Tablets 150 mcg/30mcg 7 days - EE Tablets 10 mcg
4 Seasonale	84 days - LNG/EE Tablets 150 mcg/30mcg 7 days - placebo

The duration of the study was approximately 9 months, depending on where the subject was in her menstrual cycle at the time of screening. Following the completion of the 28-day run-in cycle (Portia; 21 days of 30 mcg EE/150 mcg LNG, followed by 7 days of placebo), subjects were randomized to one of the above four treatment arms and product was administered for two consecutive 91-day extended cycles (26 weeks).

5.3.2.6 Key inclusion Criteria

1. Females aged 18-45 years old at time of screening.
2. Body Mass Index (BMI) < 35 kg/m^2
3. Agreed to use back-up non-hormonal contraception throughout the 26-week randomized treatment period.
4. Had three consecutive, regular (24-32 day) menstrual periods or withdrawal bleeding episodes immediately preceding the screening visit. Subjects using an extended cycle regimen must have completed at least one extended cycle of therapy including at least one withdrawal bleeding episode.

5.3.2.7 Key Exclusion Criteria

1. Any condition (history or presence of) which contraindicated the use of combination oral contraceptives:
2. History of alcohol or drug abuse which, in the opinion of the investigator, made the subject unfit for participation in the study
3. History of an adverse experience with oral contraceptive use

4. Smoker and age > 35 years at the time of the Screening Visit, or smokers who became 35 while taking IP; Breast feeding;
5. History of being HIV, Hepatitis B, or Hepatitis C positive
6. History of having received injectable hormone therapy (e.g. Depo-Provera) within the 10 months prior to screening or having an intrauterine device (IUD) in place within one month prior to screening or had a contraceptive implant removed within one month prior to screening
7. Use of non-contraceptive sexual hormonal therapy, administered by any route, within 3 months prior to screening
8. Subjects who had recent surgical or medical abortion, miscarriage, or vaginal or cesarean delivery must have had at least three consecutive, spontaneous menstrual cycles or withdrawal bleeding episodes prior to screening
9. Hyperlipidemia (fasting cholesterol level > 260 mg/dL or fasting triglyceride level > 300 mg/dL)
10. Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam, or any laboratory finding which contraindicates the use of oral contraceptives, would confound interpretation of study results, or put the subject at risk
11. Low-grade squamous intraepithelial lesion (LSIL) or worse on screening Pap test or any other abnormal finding on the Pap test that the investigator considered clinically significant.

Medical Officer's Comment:
The eligibility criteria were acceptable and similar to other COC trials.

5.3.2.8 Study Procedures

Table 9: Schedule of Assessments for Trial 201

	Screening	Portia Run-In	Random-ization	Two 91-Day Extended Cycles					Final Visit
	Visit 0	Visit 1	Visit 2 Wk 0	Visit 3 Wk 4	Visit 4 Wk 10	Visit 5 Wk 16	Visit 6 Wk 22	Visit 7 Wk 26	Visit 8
Informed Consent	X								
Randomization			X						
Medical/Gynecologic History	X								
Physical Exam, including Height	X								X
Vital Signs	X	X	X	X	X	X	X	X	X
Smoking History	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test		X	X	X	X	X	X	X	
Serum Pregnancy Test	X								X
Chemistry Panel/CBC/Urinalysis	X								X
Fasting Lipid Panel	X								X
Pelvic Exam/Pap test	X								X
Self-report of Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Dispense Study Diary		X	X						
Review Study Diary		X	X	X	X	X	X	X	X
Collect Study Diary			X						X
Dispense Study Drug		X	X		X				
Assess Study Drug Compliance			X	X	X	X	X	X	X
Collect Study Drug Packs				X		X			X

Visit 8: 14-21 Days Post Last Dose
Source: CSR 201 page 29

5.3.2.9 Primary end-point

The primary efficacy endpoint was total number of bleeding and/or spotting days during each 84-day active treatment cycle and each 7-day withdrawal cycle.

The secondary efficacy endpoints were total number of bleeding days during each 84-day active cycle and each 7-day withdrawal cycle.

Intent-to-Treat Cohort (ITT)
The intent-to-treat cohort (ITT) consists of all subjects who were randomized to receive treatment and who completed at least one cycle of study medication (a partial cycle in

which a subject became pregnant was considered a complete cycle). A total of 567 subjects were randomized and treated; 448 subjects were included in the ITT cohort.

Table 10: Trial 201- ITT population

	Low Dose	Midrange Dose	High dose	Seasonale	Total
All Treated (Safety)	140	136	143	148	567
At Least One Complete Cycle on Treatment (ITT)	110	110	108	120	448

Source: CSR for trial 201 page 53

The ITT cohort served as the principal subject cohort for all endpoints. An analysis of variance (ANOVA) was performed to estimate the difference between each active treatment group and Seasonale and the associated 95% confidence intervals.

5.3.2.10 Disposition of Subjects:

A total of 618 subjects were randomized; 567 subjects took at least one dose of study drug. A summary of subject disposition is presented in Table 11. In total, 406 subjects (71.6%) completed the study, 36 (6.3%) subjects discontinued the study due to subject request to be withdrawn, 35 (6.2%) subjects discontinued the study due to adverse events, and 53 (9.3%) subjects discontinued the study due to loss to follow-up.

Table 11: Subject Disposition Trial 201- Safety Cohort

	Low Dose N (%)	Midrange Dose N (%)	High Dose N (%)	Seasonale N (%)	Total N (%)
All Treated (Safety)	140	136	143	148	567
Completed Study	99 (70.7)	102(75.0)	96 (67.1)	109 (73.6)	406 (71.6)
Did Not Complete Study	41 (29.3)	34 (25.0)	47 (32.9)	39 (26.4)	161 (28.4)
Discontinued due to:					
Did Not Meet Protocol Requirements	1 (0.7)	0	2 (1.4)	0	3 (0.5)
Non-Compliance with the Protocol	2 (1.4)	4 (2.9)	9 (6.3)	7 (4.7)	22 (3.9)
Subject Request to be Withdrawn	10 (7.1)	6 (4.4)	8 (5.6)	12 (8.1)	36 (6.3)
o *Bleeding and/or Spotting Related*	6 (4.3)	2 (1.5)	3 (2.1)	7 (4.7)	18 (3.2)
Adverse Event	10 (7.1)	5 (3.7)	12 (8.4)	8 (5.4)	35 (6.2)
o *Bleeding and/or Spotting Related*	3 (2.1)	3 (2.2)	5 (3.5)	2 (1.4)	13 (2.3)
Subject Pregnant	0	1 (0.7)	2 (1.4)	2 (1.4)	5 (0.9)
Lost to Follow-Up	15 (10.7)	15 (11.0)	13 (9.1)	10 (6.8)	53 (9.3)
Other	3 (2.1)	3 (2.2)	1 (0.7)	0	7 (1.2)

Source: Table 4, CSR trial 201, page 50 Note: Numbers in parentheses are percentages of all treated (safety) subjects for each and total treatment groups.

Medical Officer's Comment:
Overall subject disposition was similar among all four groups in the trial.

5.3.2.11 Demographics:

Demographic and baseline information of the ITT subject cohort by treatment groups is summarized in Table 12. The treatment groups were comparable in demographics and baseline characteristics for all parameters. Mean age was 30.5 years. The majority (65.0%) of subjects were Caucasian. Mean BMI was 25.9 kg/m^2. A total of 333 (74.3%) subjects were non-smokers and 76 (17.0%) subjects were new-start users of OCs.

Table 12: Demographics in Trial 201

	Low Dose	Midrange Dose	High Dose	Seasonale	Total
N	110	110	108	120	448
Age: Mean (SD)	30.1 (6.9)	30.5 (7.0)	30.7 (7.6)	30.6 (6.9)	30.5 (7.1)
BMI: Mean (SD)	26.6 (4.1)	25.7 (4.2)	26.0 (4.6)	25.5 (4.4)	25.9 (4.4)
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
African-American	21 (19.1)	20 (18.2)	18 (16.7)	17 (14.2)	76 (17.0)
Asian	1 (0.9)	4 (3.6)	1 (0.9)	3 (2.5)	9 (2.0)
Caucasian	72 (65.5)	68 (61.8)	69 (63.9)	82 (68.3)	291 (65.0)
Hispanic	13 (11.8)	17 (15.5)	19 (17.6)	16 (13.3)	65 (14.5)
Other	3 (2.7)	1 (0.9)	1 (0.9)	2 (1.7)	7 (1.6)
Current Smoker	13 (11.8)	16 (14.5)	11 (10.2)	11 (9.2)	51 (11.4)
OC Use History					
Continuous User	44 (40.0)	46 (41.8)	42 (38.9)	49 (40.8)	181 (40.4)
Prior User	44 (40.0)	45 (40.9)	49 (45.4)	52 (43.3)	190 (42.4)
Fresh-Start	21 (19.1)	19 (17.3)	17 (15.7)	19 (15.8)	76 (17.0)

Source: Table 6, CSR trial 201, page 54,55

Medical Officer's Comment:
The results of bleeding/spotting data, the primary endpoint for Trial 201, are presented in Section 7.3.4, along with bleeding/spotting data from Trial 301. Based on evaluation of the bleeding profiles demonstrated in the various dose regimens evaluated, the Applicant chose the "low dose" regimen to study in phase 3.

6 Review of Efficacy

Efficacy Summary

Efficacy was based on the Pearl Index (PI) using all "on-drug" pregnancies. On-drug pregnancies were defined as those pregnancies for which conception occurred on or after the date of first intake of study drug and extending through 7 days following the last tablet (whether a combination or EE-alone tablet). The PI was derived from the PITT, which consisted of all women ages 18-35 who completed at least one 28-day cycle of therapy. All 28-day cycles where additional back-up methods of birth control (including condoms) were used and all incomplete 28-day cycles (except those in which conception occurred) were excluded.

As determined by the medical and statistical reviewers, 70 on-drug pregnancies occurred in the PITT population over 28,515 completed 28-day cycles where no other back-up method of birth control was used. The Pearl Index was 3.19 (95% CI: 2.49, 4.03) per 100 women-years of use.

Medical Officer's Comments:

- ***A minimum of 10,000 28-day cycles are usually studied for COCs, therefore the 28,515 28-day cycles studied in this NDA are considered sufficient for determining efficacy. The Pearl Index of 3.19 is acceptable to support the efficacy of Quartette.***
- ***Even though this was a 91-day cycle regimen, the Division typically evaluates PI according to 28-day cycles as this approach retains more data. If another birth control method is used, only 28 days of data, rather than 91 days, need to be excluded as unevaluable.***

With increasing weight the Pearl Index increased (For women ≥90 kg, the PI was 4:82 (2.86-7.6). The Pearl Index was consistently higher in African American (AA) women compared to non-AA women. These findings held true even when the analysis was stratified by weight. For AA women < 70 kg, the PI was 5.37 while for non-AA women < 70 kg, the PI was 2.19. For AA women ≥ 90 kg, the PI was 6.64 while for non-AA women ≥ 90 kg, the PI was 4.1. Therefore, race seems to be an independent risk factor for higher pearl index.

6.1 Indication

For prevention of pregnancy in women of reproductive age at risk for pregnancy who desire contraception.

6.1.1 Methods

Because there is only one phase 3 efficacy study, this section of the review will focus entirely on information from that study; there are no pooled findings.

The key sections from NDA 204061 regarding contraceptive efficacy were found in:

- Clinical Overview
- Clinical Study Report for Trial 301

Demographics

Approximately 65% of all treated subjects were Caucasian, 19% were African-American, and 11% were Hispanic. The mean age was 27.1 years, the mean weight was 162.5 pounds, and the mean body mass index (BMI) was 27.4 kg/m^2. Over 80% of the subjects were non-smokers, and most were either continuous users (44%) or prior users (39%) of oral contraceptives.

Table 13: Demographic characteristic of subjects in Trial 301

Parameter	Safety (N = 3597)		ITT (N = 3352)		PITT (N=3019)	
Mean Age (years)	27.1		27.1		25.9	
Body Mass Index (kg/m2)Mean	27.4		27.4		27.2	
Race	**N**	**%**	**N**	**%**	**N**	**%**
American Indian or Alaska native	14	0.4	14	0.4	12	0.4
Asian	78	2.2	75	2.2	70	2.3
Black	696	19.3	633	18.9	550	18.2
Native Hawaiian	10	0.3	10	0.3	10	0.3
White	2324	64.6	2181	65.1	1977	65.5
Hispanic	404	11.2	371	11.1	335	11.1
Other	71	2.0	68	2.0	65	2.2
Contraceptive History						
Continuous User	1570	43.6	1509	45.0	1337	44.3
New start	619	17.2	555	16.6	523	17.3
Prior user	1408	39.1	1288	38.4	1159	38.4
Smoking History						
Currently	602	16.7	550	16.4	549	18.2
Former	636	17.7	601	17.9	529	17.5
Never	2359	65.6	2201	65.7	1941	64.3

Source clinical study report for Trial 301, page 55.

Medical Officer's Comment:
Adequate numbers of non-Caucasians were studied, as well as women over 35 years of age (who mainly contribute to the safety database). There was no entry restriction based on BMI. The range of BMI was 15.5 - 64.7.

Subject Disposition

A total of 4,962 subjects were screened for participation in this study and 3,701 were enrolled (1,261 were screen failures). There were no major differences in age and race of the subjects who were enrolled vs. screen failures.

Of those enrolled, 3,597 (97.2%) subjects took at least one dose of IP (Safety population). Of the 3,597 subjects who started treatment, a total of 3,352 (93.2%) completed at least one 28-day cycle-equivalent of IP use (ITT population). Of the 3,352 subjects in the ITT population, a total of 3,019 (90.1%) were between 18 and 35 years of age (PITT population).

A total of 2,144 treated subjects (59.6%) completed the study. Table 14 summarizes the reasons for discontinuation. The most common reasons for discontinuation were AEs (13.0%) and loss to follow-up (13.3%). AEs related to bleeding and/or spotting accounted for about one-third of the reported AEs that led to discontinuation. Approximately 6.0% of the subjects requested to be withdrawn from the study.

Table 14: Disposition in Trial 301

Screened	4,962
Enrolled	3,701 (1,261 screen failures)
Safety population (subjects took at least one dose of IP)	3,597 (100%)
Intent to Treat population	3,352 (93.2%)
Pregnancy Intent to Treat population	3,019 (90.1%)
Completed Study	2,144 (59.6%)
Discontinued Study Prematurely	1,453 (40.4%)
Primary Reason for Discontinuation:	
Adverse Event	466 (13.0%)
—Bleeding and/or Spotting Related	168 (4.6%)
Lost to Follow-Up	480 (13.3%)
Noncompliance with the Protocol	137 (3.8%)
Investigator Discretion	5 (0.1%)
Pregnancy	68 (1.9%)
Protocol Violation	16 (0.4%)
Applicant Requested Subject's Withdrawal*	35 (1.0%)
Subject Requested to be Withdrawn	217 (6.0%)
Other	28 (0.8%)

Source: Applicant table 3, CSR trial 301, page 51 and reviewer re-assignment of some disposition events after evaluating reasons for termination in detail.
* includes the site LA0012 subjects

Medical Officer's Comment:

- ***The overall discontinuation rate for Quartette in the Safety cohort of 3,597 subjects was 40.4%. This percentage is similar to one-year trials of other extended cycle OCs. For LoSeasonique (NDA 22-262), this rate was 42.8%. Seasonale (NDA 21-544) had an overall discontinuation rate in the Safety cohort of 40.6% and Seasonique (NDA 21-840) had a discontinuation rate in the Safety cohort of 50.3%. The discontinuation rate for Lybrel was 56.8%.***
- ***A total of 2,144 subjects completed treatment over one year. This exceeds the FDA recommended subject exposure, which was 200 women for ≥ 12 months in order to adequately assess safety.***

Some disposition events were miscoded. For example, Subject-10053020 discontinued the study because the frequency of breakthrough bleeding was unacceptable to subject, but this was coded as "other."

The biggest discrepancy was found when the "subject request" category was analyzed in detail as shown in Table 15.

Table 15: Subject Disposition reported as 'Withdrawal by subject' but the disposition terms suggest too much bleeding-spotting and other reasons

Unique Subject Identifier	Reported Term for the Disposition Event
Due to Bleeding/Spotting	
PA-0006-10006008	Due to breakthrough bleeding
NC-0081-10081007	Due to concern about gaining weight
NC-0081-10081021	Due to continual spotting/bleeding
NC-0081-10081015	Due to experiencing excessive spotting/bleeding between cycles.
KY-0049-10049006	Due to spotting continuously
TN-0084-10084033	She withdrew consent after 15 days of drug due to spotting and bleeding during this time.
FL-0034-10034195	Subject complained of excessive spotting/bleeding.
NC-0063-10063043	Subject did/does not like having her period every 3 months due to when she does have her period it lasts longer per patient.
WA-0053-10053100	Subject felt it was difficult to lose weight while taking the study medication.
TN-0035-10035006	Subject had 38 days of spotting and bleeding
WA-0053-10053056	Subject withdrew consent due to breakthrough bleeding
TX-0079-10079061	Subject withdrew consent, she said that her physician advised her that the pills were causing her bp to be elevated.
TN-0035-10035044	Subject withdrew due to 19 days straight of bleeding
NY-0018-10018037	Subject withdrew due to too much spotting per diary
Due to Other Reasons	
NJ-0091-10091013	Subject withdrew because of side effects of oily hair, acne, and diminished sex drive.
TN-0035-10035004	Acne vulgaris, was to be put on antibiotics long term.
OH-0071-10071081	Decided to begin long term antibiotic therapy for ongoing acne
NC-0073-10073051	Due to migraine headaches
TN-0038-10038007	Patient did not like how she felt on pill
DC-0082-10082013	Perceived weight gain
NJ-0091-10091048	Subject claimed ip gave her anxiety
CA-0028-10028024	Subject wanted to withdrew due ip due to her belief that the ip was making her feel not well.

Source: Medical Officer's analysis of the DS dataset using JMP program

Medical Officer's Comment:

- ***Adding these miscoded subjects who actually had bleeding/spotting as the reason for withdrawal) to the "discontinuation due to AE" category increases the percent of subjects discontinuing from the study due to bleeding/spotting from 4.6% to 5%. While this miscoding is undesirable, overall, this rate was similar to other combined oral contraceptives. In NDA 22-262, 9.6% subjects discontinued LoSeasonique, at least in part, due to bleeding and/or spotting.***
- ***In NDA 22-262 (LoSeasonique), similar miscoding was observed. In the Safety Cohort, 94 of the 225 subjects (42%) in the "Subject Request" group cited bleeding and/or spotting as contributing to the decision to withdrawal.***

6.1.4 Analysis of Primary Endpoint(s)

In the original submission, the Applicant reported 65 pregnancies as "on-drug" pregnancies. However, the Applicant used the definition of "on-drug" pregnancy as all pregnancies conceived within seven days after intake of the last combination pill.

The Division clarified that the Pearl Index calculation should include all pregnancies conceived within 7 days after intake of the LAST TABLET – whether it is a combined EE/LNG tablet or EE alone. An incomplete 28-day cycle in which a subject became pregnant should be considered a complete cycle for all pregnancy calculations. Evaluable cycles should exclude any 28-day cycle in which back-up contraception was used.

On 9/28/2012, the Applicant agreed to this definition and reported 67 pregnancies as "on-drug" pregnancies.

Upon detailed review, The statistical reviewer and I identified three more pregnancies that should be counted as "on-drug" pregnancies under a "worst-case" approach. The details of these three pregnancies are as follows:

- Subject FL-0001-10001115 began the IP regimen on July 25, 2010 and made her last study visit on August 18, 2010. She contacted the study site by telephone on January 3, 2011 to state that she had a positive home urine pregnancy test on December 20, 2010. Subsequent review of medical records revealed that the subject had had a pelvic examination and ultrasonography on November 30, 2010 as well as a serum pregnancy test on December 9, 2010. The ultrasound revealed a single viable fetus with an estimated gestational age (EGA) of 6 weeks 3 days. This reviewer calculated an estimated date of conception based on the EGA and a standard obstetric wheel of October 30, 2010 (not November 1). The stop date for study drug was estimated to be October 23, 2010, based on her start date and the number of tablets dispensed. Consequently, according to this reviewer's calculations, conception occurred within 7 days after her likely last intake of investigational product. Because the Division uses a "worst case scenario" approach in counting on-treatment

pregnancies where information is not absolutely clear, this is considered an on-treatment pregnancy.

- Subject MD-0005-10005055 began the IP regimen on May 2, 2010. Urine pregnancy tests were negative through Visit 7 on January 24, 2011. The subject was lost to follow-up; however, on April 4, 2011, the subject contacted the study site by telephone to report that she was pregnant. The audit history (CRF page 70) states that on July 20, 2011, the date of last dose of the study drug was changed from unknown to March 22, 2011, but later, in August 2011, it was changed back to blank as the pregnancy eCRF noted that the date of last dose of study drug was unknown. The CRF also notes that Cycle 4 was dispensed (page 205 of CRF). Based on pills dispensed at Visit 7, she should have had a supply of the study drug lasting till May 1, 2011. Therefore, in the worst case scenario approach, this pregnancy is considered on-treatment.
- Subject NC-0042-10042029 began to take the IP regimen on November 29, 2009. The subject reported stopping study drug on January 19, 2010. Transvaginal ultrasonography was performed on March 18, 2010 and estimated a gestational age of 9 weeks 2 days. This reviewer calculated an estimated date of conception based on the ultrasound dating and using a standard obstetric wheel of January 26, not January 27, 2010. Therefore, the Division considers it an on-treatment pregnancy.

Table 16 presents the Pearl Index results for complete 28-day cycle-equivalents for Quartette in the PITT population according to the Applicant's and FDA's calculations.

Table 16: Summary of Pearl Index analyses for complete 28-day cycle-equivalent – PITT population

	N	Number of On-Drug Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete 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 1, 8.3 in response-to-fda-set-2.pdf Appendix B/reviewer's analysis.

Medical Officer's Comments:

- ***Two of the additional pregnancies identified by the Division were cases in which the Applicant's and FDA's calculation of the conception date differed by a single day. Obstetric wheels are not precise, and a case could be made for either date; however, all other conception dates (for 68 pregnancies) determined using the same wheel matched with the Applicant's dates. For this reason, the Division considered these two cases likely to have occurred on-drug.***
- ***This PI is on the higher side, but it is within the range of other approved***

NDA's. The PI for recently approved COCs are as follows:

LoSeasonique (NDA 22-262, extended cycle): 2.74 (95% CI: 1.92, 3.78)
Seasonale (NDA 21-544, extended cycle): 1.97 (95% CI: 0.54, 5.03)
Seasonique (NDA 21-840, extended cycle): 1.77 (95% CI: 0.7, 3.64)
Lybrel (NDA 21-864, extended cycle): 2.39 (95% CI: 1.57, 3.62)
Lo Loestrin Fe NDA 22-501): 2.92 (95% CI 1.94, 4.21)

- ***The upper bound of the 95% CI for this NDA is lower than that for Seasonale and Lo Loestrin FE.***

Table 17 presents the Pearl Index results for 91-day cycles for Quartette in the PITT population. The Applicant-reported Pearl Index is 3.37 (95% CI: 2.61-4.27).and the reviewer-reported Pearl Index is 3.52 (95% CI: 2.75-4.44).

Table 17: Summary of Pearl Index analyses for complete 91-day cycles – PITT population

	N	Number of On-Drug Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
Applicant	2747	67	9,164	1207	7,957	3.37	(2.61, 4.27)
Reviewer	2747	70	9,164	1207	7,957	3.52	(2.75, 4.44)

Site LA0012 is excluded.
Source: Table 1, 8.3 in response-to-fda-set-2.pdf Appendix B/reviewer's analysis.

Medical Officer's Comments:

- ***PIs based on extended cycles will typically be higher than those based on 28-day cycles because use of back-up contraception at any point within a cycle results in the entire 91-day cycle being considered unevaluable, thus, decreasing the denominator of time at risk of pregnancy.***
- ***For a detailed table that includes all pregnancies (on-drug, off drug, in the PITT and non-PITT populations) reported in Trial 301, please refer to Table 35, at the end of the review.***

6.1.5 Analysis of Secondary Endpoints(s)

In addition to the PI calculation, a life table approach was used to estimate the cumulative pregnancy rate on a cycle-by-cycle basis for the PITT. The statistical reviewer's estimated life table pregnancy rate in all treated subjects 18-35 years of age using 70 pregnancies and all 91-day cycles is 2.85% (95% CI from 2.25% to 3.61%), and 2.82% (95% CI from 2.22% to 3.57%) using all 28-day-equivalent cycles.

By excluding site LA0012, the Applicant's estimated life table pregnancy rate in all treated subjects 18-35 years of age using 67 pregnancies and all 91-day cycles is

2.72% (95% CI 2.13% to 3.46), and 2.69% (95% CI 2.11% to 3.42) using all 28-day equivalent cycles.

6.1.6 Other Endpoints

The summary conclusions from Applicant's secondary endpoints of bleeding and overall safety are discussed in the safety section (Section 7.3).

6.1.7 Efficacy in Subpopulations

Weight: With increasing weight the Pearl Index increased as shown in Table 18.

Table 18: Effect of race and weight on the Pearl Index

Body weight	N	# on –drug pregnancies	Number of cycles	Number of BCM* cycles	Number of Complete cycles	Pearl Index	95% CI
<70 kg	1,607	31	16,525	940	15,585	2.59	(1.76, 3.67)
≥ 70 to < 90 kg	850	21	8,644	572	8,072	3.38	(2.09, 5.17)
≥ 90 kg	535	18	5,194	336	4,858	4.82	(2.86, 7.60)

* BCM=cycles in which a back-up method of contraception was used
Source: The biopharm reviewer's analysis (Dr. Florian)

Race: the Pearl Index was consistently higher in African American women compared to non-African-American women. These findings held true even when the analysis was stratified by weight. Therefore, race seems to be an independent risk factor for higher pearl index.

Table 19: Effect of race and weight on the Pearl Index

Body weight	N	# on-drug pregnancies	Number of cycles	Number of BCM cycles	Number of Complete cycles	Pearl Index	95% CI
African American							
<70 kg	210	8	2,069	133	1,936	5.37	(2.32; 10.56)
≥ 70 to < 90 kg	170	7	1,614	116	1,498	6.07	(2.44; 12.49)
≥ 90 kg	168	7	1,503	132	1,371	6.64	(2.67; 13.64)
Non-African American							
<70 kg	1397	23	14,456	807	13,649	2.19	(1.39; 3.29)
≥ 70 to < 90 kg	680	14	7,030	456	6,574	2.77	(1.51; 4.64)
≥ 90 kg	367	11	3,691	204	3,487	4.10	(2.05; 7.33)

Source: The biopharm reviewer's analysis (Dr. Florian)

Medical Officer's Comment:
The confidence intervals for the race subgroup analysis are wide. I think that is because the trial was not powered to find this difference. The trend is suggestive of race as an independent risk factor for higher PI. Race can also be a surrogate of other factors that might affect PI, such as compliance, socioeconomic factors, etc.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is no clinical issue with the dosing regimen and administration of Quartette.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

The Clinical Study Report for the primary clinical trial (DR-103-301) was submitted for review. In this study, a total of 2,144 subjects completed one year of treatment with Quartette. This exceeds the minimum Division recommendation of 200 women completing one year of treatment to adequately evaluate safety.

- There were no deaths reported.
- There were 3 VTEs on IP reported in Trial 301.
- The most common AE during the trial was headache, which occurred in 457 subjects (12.2%).
- Bleeding/spotting related AEs were the most common AEs leading to discontinuation. In Trial 301, 4.5-5% of subjects discontinued due to bleeding and/or spotting.
- Despite the prolonged number of days of unanticipated bleeding/spotting, it appears that the quantity of blood loss with this bleeding is not clinically significant. Mean hematocrit and hemoglobin values remained stable during the study.
- There were no notable changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, weight or temperature) over time within or between the treatment groups.

- There were no new signals or unexpected serious adverse events related to the use of Quartette.

Based on the data reviewed, Quartette was associated with an acceptable overall safety profile.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The key sections from NDA 204061 regarding safety were found in:

- Clinical Overview
- Summary of Clinical Safety
- Study Report for Trial 301
- Study Report for Trial 201
- Four-month safety update
- Integrated Summary of Safety report and datasets

7.1.2 Categorization of Adverse Events

The Applicant defined an AE as any untoward medical occurrence in a subject, an unfavorable sign, symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Clinical laboratory results that are outside of the normal ranges and are deemed clinically significant by the investigator were also considered AEs.

In the study, any event occurring after the clinical trial subject signed the study Informed Consent (ICF) were recorded and reported as an AE. Those events occurring prior to enrollment were considered to be “Non-Treatment-Emergent” AEs and those occurring post-enrollment as “Treatment-Emergent” AEs.

AEs were coded using the Medical Dictionary of Regulatory Authorities (MedDRA). Datasets included System Organ Class (SOC), Lowest Level Term (LLT) and Preferred Term (PT). The Applicant used two different MedDRA versions for the Integrated Summary of Safety (ISS) datasets: Version 9.0 for Trial 201 and Version 14.0 for Trial 301. Upon request, the Applicant submitted the ISS datasets using unified MedDRA coding (all adverse events coded in MedDRA Version 15) to enable integrated analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Division required at least 200 subjects completing 13 cycles and a minimum of 10,000 28-day cycles. The Applicant submitted data on 2,183 subjects who completed 13 cycles. Overall, this provided data on the equivalent of 34,354 (28-day) cycles of exposure, which is acceptable for evaluation.

7.2.2 Explorations for Dose Response

In the phase 2 Study 201, a prospective, multicenter, double-blinded, randomized trial, the Applicant evaluated bleeding patterns in women using three different ascending EE dose extended cycle (91-day) oral contraceptive regimens compared to Seasonale in 567 women (448 completed at least 1 cycle).

As shown in Table 20, the regimens in this phase 2 study had the same annual amount of levonorgestrel as the approved products Seasonale and but had different doses of annual ethinyl estradiol. The Applicant took the low ascending dose into phase 3 trial.

Table 20: Phase 2 regimen annual doses

Product (LNG mcg/EE mcg)	Annual amount of EE (mcg)	Annual amount of LNG (mcg)
Group 1, low ascending dose	8,260	50,400
Group 2, mid-range ascending dose	8,680	50,400
Group 3, high ascending dose	9,100	50,400
Group 4, Seasonale (150/30)	10,080	50,400

The incidence of treatment-emergent adverse events, treatment-related adverse events and serious adverse events appeared to be comparable among all 4 groups. There were no observed clinically relevant differences between each ascending EE dose regimen and Seasonale for any laboratory tests or vital signs measurements.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was indicated or required.

7.2.4 Routine Clinical Testing

The routine clinical testing for this NDA was adequate. No special metabolic, clearance and interaction workup was required for this NDA.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The data submitted to the NDA was adequate for the evaluation for potential adverse events. No recommendations for further study are necessary.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the clinical trials for this product.

Nonfatal Serious Adverse Events

This analysis presents data for the integrated safety population (Trials 301 and 201). Overall, 59 of the 3,737 subjects in the low dose [Quartette] group (2%) had 78 serious adverse events. This compares to 2 subjects (1%) with 3 events in the midrange dose group, 2 (1%) subjects with 3 (2%) events in the high dose group and 5 (3%) subjects having 7 events in the Seasonale group.

Table 21: Serious adverse events in ISS dataset by body system organ class

System Organ Class and Adverse Event	Arm	N
Infections and Infestations		
Appendicitis, Pneumonia, Pyelonephritis, Viral infection	Low Dose	2 each, total 8
Helicobacter gastritis, Hepatitis C, Pelvic inflammatory disease, Pharyngitis, Rectal abscess, Salpingitis, Staph infection, UTI	Low Dose	1 each, total 8
Pyelonephritis	Midrange Dose	1
Pregnancy, Puerperium and Perinatal Conditions		
Abortion spontaneous	Low Dose	5
Abortion spontaneous	High Dose	2
Abortion missed, Ectopic pregnancy	Low Dose	2 each, total 4
Blighted ovum, Premature separation of placenta	Low Dose	1 each, total 2
Ectopic pregnancy	Seasonale	1
Injury, Poisoning and Procedural Complications		
Overdose	Low Dose	2
Road traffic accident	Seasonale	2
Injury, Joint injury, Lower limb fracture, Multiple drug overdose, Spinal fracture	Low Dose	1 each, total 5

Multiple fractures, polytraumatism	Seasonale	1
Post procedural bile leak	Midrange Dose	1
Psychiatric Disorders		
Suicide attempt	Low Dose	5
Anxiety, Depression, Depression suicidal, Drug dependence, Mental status changes	Low Dose	1 each, total 5
Gastrointestinal Disorders		
Abdominal pain	Low Dose	3
Gastrointestinal haemorrhage	Low Dose	2
Colitis, Ileitis	Low Dose	1 each, total 2
Small intestinal obstruction, vomiting	Seasonale	1 each, total2
Hepatobiliary Disorders		
Cholelithiasis, Cholecystitis	Low Dose	3 each, total 6
Cholecystitis	Midrange Dose	1
Nervous System Disorders		
Convulsion	Low Dose	3
Hemiparesis ,Hypoaesthesia	Low Dose	1 each, total 2
Headache, Syncope	Low Dose	1 each, total 2
Musculoskeletal and Connective Tissue Disorders		
Bursitis, intervertebral disc protrusion, Pain in extremity	Low Dose	1 each, total 3
Intervertebral disc protrusion	High Dose	1
Cardiac Disorders		
Angina pectoris, Supraventricular tachycardia, Atrial fibrillation	Low Dose	1 each, total 3
Vascular Disorders		
Deep vein thrombosis	Low Dose	3
Respiratory, Thoracic and Mediastinal Disorders		
Pleural effusion	Low Dose	1
Pulmonary embolism	Low Dose	1
Other SOCs: Anaemia, Hip dysplasia, Uterine inflammation	Low Dose	1 each, Total 3

Source: Medical Officer analysis of Adverse Event dataset using JMP program.
Low-dose is the same as to-be-marketed dose (Quartette). Subjects in Trial 301 received this 'low-dose' regimen. The low-dose arm in the table includes subjects from Trial 301 and one arm (out of 4) of Trial 201.

Medical Officer's Comments:

- ***Deep vein thrombosis was reported in 3 subjects receiving the Quartette and are described in Section 7.5.3.***
- ***No AE associated with vaginal bleeding and/or spotting was considered serious.***

- ***These serious adverse events have been previously reported in association with COCs. There are no new safety signals.***
- ***There were 6 suicide attempts/ideations, described below in detail.***

1. Subject 10040-008 ([(b) (6)]) Drug Overdose; Attempted Suicide

A 27 year-old Caucasian female with history of hyperemesis gravidarum, tension headaches, insomnia, and acne was a prior user of oral contraceptives. The subject began the IP regimen on 20 June 2010. On [(b) (6)] the subject was evaluated in an emergency department with episodes of crying and feelings of depression and decreased concentration. One hour prior to presentation, the subject had ingested 30 Prozac and 15 Klonopin pills and admitted that the ingestion was a suicide attempt. A 12-lead EKG demonstrated no QT prolongation. The subject was treated with 50 grams of activated charcoal with sorbitol and parenteral hydration. The subject disclosed that she had a prior history of self-mutilation and had experienced previous bouts of depression and suicidal ideation. Additionally, she noted that child custodial issues had precipitated the recent attempted suicide. The subject also noted that she had been previously treated for anxiety and depression and had received a prescription for fluoxetine 40 mg once daily on 10 August 2010. The subject was transferred to the crisis stabilization unit at a behavioral center. The subject's last dose of study drug was on an unspecified date in 2010. The subject has been lost to follow-up and the study site has been unable to contact the subject. No further information is available.

2. Subject 10051-054 ([(b) (6)]) Depressive Episode-Overdose-Attempted Suicide

An 18 year-old Caucasian female was a new start user of oral contraceptives. The medical history included anxiety, impulsive disorder, and generalized muscle ache. No concomitant medications. The subject began the IP on 7 March 2010. The subject was brought to the emergency department on [(b) (6)] by a family member after she attempted to strangle herself with a blanket. She was admitted to a psychiatric hospital and reported experiencing intermittent shortness of breath as well as a previous suicide attempt by ibuprofen ingestion 2 to 3 weeks prior to admission. The subject was placed on Celexa 20 mg daily and Haldol 0.5 mg twice daily for a depressive episode and was discharged on [(b) (6)]. On [(b) (6)], the subject ingested approximately 50 tablets of Haldol 0.5 mg and denied this was a suicide attempt. In the emergency department, the subject received Zofran 4 mg and two gastric lavages with 300 cc activated charcoal. The EKG demonstrated sinus tachycardia with a QT_C interval of 461 msec. The Glasgow Coma Scale score was 15. The urine drug screen was positive for cannabinoids. However, the subject denied using cannabinoids. On [(b) (6)], subject was discharged from the hospital and was transferred back to the psychiatric hospital. She was placed on Trazodone 50 mg at bedtime and Pristiq 50 mg daily. The subject completed the study and took her last dose of study drug on 5 March 2011 and had her last visit on 28 March 2011, at which her vital signs were stable and the urine pregnancy test result was negative.

3. Subject 10053-086 ([(b) (6)]) Suicide Attempt-Polysubstance Overdose

A 22 year-old Caucasian female; nulligravida; was a prior user of oral contraceptives. Medical history included menstrual cramps, Chlamydia infection, depression, impulsivity, and attention deficit disorder. Concomitant medications included Celexa and Topamax. The subject began the IP regimen on 18 April 2010. On [(b) (6)] the subject presented to an emergency

department after an apparent suicide attempt. Upon arrival she was somnolent but arousable with stable vital signs. The subject's partner stated that she consumed large quantities of alcohol and ingested prescription medications, including 10 tablets of Percocet 5/500; 8-10 tablets of Topamax (unknown strength) and 10-15 40 mg tablets of citalopram. A plasma acetaminophen level was elevated at 40. The initial 12-lead ECG showed QTc interval prolongation at 496 msec. She was treated with lorazepam and ondansetron. Her partner stated she has been very emotional lately due to social stressors and has been followed by a psychiatrist for bipolar disorder. The subject recovered and was discharged on (b) (6). The subject completed the study and took her last dose of study drug on 23 April 2011 and had her last visit on 05 May 2011, at which her vital signs were stable and the urine pregnancy test result was negative.

4. Subject 10092-012 ((b) (6)) Attempted Suicide with Drug Overdose

A 21 year-old Caucasia female; nulligravida; non- smoker, was a continuous user of oral contraceptives. Her medical history included tonsillectomy, intermittent cystitis, menstrual cramps, mild acne, and mastalgia. The subject began the IP on 6 December 2009. On (b) (6), the subject presented to an emergency department after overdosing on ibuprofen (approximately ten 200 mg tablets) and Hydromet cough syrup (hydrocodone/homatropine, approximately 80 ml). The subject's symptoms on presentation included headache, nausea, and vomiting. The subject had a positive screen for opiates and received activated charcoal 25 gm orally, ondansetron 4 mg IV, and promethazine 25 mg IV. She was discharged from the emergency department then sent to a crisis center. The subject was discharged on (b) (6) from the crisis center on Abilify 10 mg daily. The subject's depression did not improve on Abilify. She was then prescribed Prozac. During the course of the study she experienced dizziness and insomnia which was severe; she was treated with Prozac and Ativan. Both events were ongoing. The subject was subsequently withdrawn from the study due to the attempted suicide; she completed the final study visit on 20 January 2010.

5. Subject 10092-017 ((b) (6)) Suicidal Thoughts with Drug Overdose

A 27 year-old Caucasia nulligravida female was a continuous user of oral contraceptives. The medical history included menstrual cramps, intermittent candidiasis, intermittent cystitis, anxiety, depression, insomnia, and reaction to Ambien CR. The subject began IP on 23 November 2009. On (b) (6) the subject reported to study investigator that she was feeling sad and had suicidal thoughts. In addition, she stated on (b) (6) she slit her left wrist and took Ambien, Tylenol PM, and Flexeril and some alcohol and went to bed. Subject went to an emergency room on (b) (6) for evaluation and treatment of the cut to the left wrist which was superficial and required no treatment. The subject was admitted for observation. She admitted she was not trying to kill herself. The subject was discharged from the hospital on (b) (6), and given coping skills to use when stressed. The subject discontinued the study due to the severe adverse event and took her last dose of study drug on 19 February 2010 and had her last study visit on 10 March 2010, at which her vital signs were stable and the urine pregnancy test result was negative.

6. Subject 10095-019 ((b) (6)) Depression Worsening with Suicidal Ideation

A 21 year-old Caucasian female was a prior user of NuvaRing hormonal contraceptive. Medical history included overactive bladder, severe dysmenorrhea, seizure, migraine

headache (ocular type without other neurological signs or symptoms, intermittent and severe), acne, depression, anxiety, Chlamydia infection, and allergy to Zyprexa and codeine. Concomitant medications include Paxil. The subject began the IP on 13 December 2009. On (b) (6), the subject was taken to the emergency department after reportedly consuming a large amount of alcohol, and taking a multiple tablets (capsules) of Concerta and Klonopin. The subject had a blood alcohol level of 0.18 and received activated charcoal. Urine drug screen was negative and salicylate and acetaminophen levels were non-detectable. She was admitted to the hospital due to worsening depression with suicidal ideation. She received Wellbutrin 150 mg twice daily, Celexa 40 mg daily, Klonopin 0.5 mg three times daily, Aciphex 20 mg daily, trazodone 100 mg at bedtime, potassium chloride 40 mEQ (one dose) followed by 10 mEQ daily, Concerta 18 mg, and Milk of Magnesia. The subject was discharged from the hospital on (b) (6). The subject was subsequently lost to follow-up and did not complete the study.

Medical Officer's Comment:
Although some of these subjects had a history of major depression prior to the study, this reviewer cannot rule out a worsening of the condition with study drug. The progestin component of COCs is thought to be related to depression and mood changes.

In 2007, the background suicide rate among young women age 14-25 was 3.2 per 100,000 and 4.8 per 100,000, for all women[1]. The expected number of suicides in the clinical trial of 3,701 women would be <1. According to a CDC 2012 fact sheet, there is one suicide for every 25 attempted suicides. An estimated 1 million adults (0.3% of the U.S. adult population) reported making a suicide attempt in the past year[2]. Expected suicide attempts in the clinical trial of 3,701 women would be about 11-12. Due to selective eligibility criteria, the clinical trial population may be healthier compared to general population. Therefore, in a single arm study it is hard to assess risk of suicide. Overall, there does not appear to be a higher risk of suicidality compared to the background rate.

7.3.3 Dropouts and/or Discontinuations

The adverse events leading to discontinuation are shown in Table 22 and further detailed in Table 23.

[1] http://www.afsp.org/files/College_Film//factsheets.pdf
[2] http://www.cdc.gov/violenceprevention/pdf/suicide-datasheet-a.PDF

Table 22: Adverse Event leading to discontinuation occurring in ≥ 5 subjects, by system organ class (SOC)

Adverse events leading to drug discontinuation	**Quartette (N = 3,737)**		
SOC	**Events**	**Number of subjects**	**%**
Reproductive system and breast disorders	222	204	5.5
Psychiatric disorders	97	87	2.3
Investigations	60	59	1.6
Gastrointestinal disorders	66	52	1.4
Skin and subcutaneous tissue disorders	57	52	1.4
Nervous system disorders	59	51	1.4
General disorders and administration site conditions	34	29	0.8
Metabolism and nutrition disorders	12	12	0.3
Musculoskeletal and connective tissue disorders	12	11	0.3
Vascular disorders	10	10	0.3
Infections and infestations	6	6	0.2
Cardiac disorders	5	5	0.1
Eye disorders	5	5	0.1

Source: Medical Officer's analysis of ISS Adverse Event dataset using MAED program

Medical Officer's Comment:
Adverse events leading to discontinuations occurred most frequently in the reproductive system organ class.

Table 23: Adverse Events leading to drug discontinuation by preferred term

	Quartette (N = 3737)		
PT	**Events**	**Number of subjects**	**%**
Metrorrhagia	**107**	**107**	**2.9**
Vaginal haemorrhage	**59**	**55**	**1.5**
Weight increased	47	47	1.3
Acne	37	34	0.9
Headache	33	31	0.8
Mood swings	29	28	0.8
Nausea	29	28	0.8
Mood altered	19	17	0.5
Migraine	17	15	0.4
Depression	12	12	0.3
Abdominal distension	12	10	0.3
Irritability	10	10	0.3
Affect lability	10	9	0.2
Fatigue	10	9	0.2
Anxiety	8	8	0.2
Blood pressure increased	8	8	0.2
Dysmenorrhoea	8	8	0.2
Hypertension	8	8	0.2
Libido decreased	8	8	0.2
Menorrhagia	**8**	**8**	**0.2**
Alopecia	7	7	0.2
Breast tenderness	7	7	0.2
Increased appetite	6	6	0.2
Abdominal pain lower	5	5	0.1
Pelvic pain	6	5	0.1
Abdominal discomfort	4	4	0.1
Abdominal pain	4	4	0.1
Chest pain	4	4	0.1
Cervical dysplasia	3	3	0.1
Dizziness	4	3	0.1
Palpitations	3	3	0.1
Premenstrual syndrome	3	3	0.1

Source: Medical Officer's analysis of ISS Adverse Event dataset using MAED program

Medical Officer's Comment:
Adverse events related to bleeding and spotting were coded using different preferred terms such as Metrorrhagia, Menorrhagia and vaginal hemorrhage. The combined incidence was 4.54%.

7.3.4 Significant Adverse Events (Bleeding/spotting)

The most significant adverse events in terms of incidence were the bleeding problems of menorrhagia and intermenstrual bleeding. Both trials, the phase 2 dose-finding trial (201) as well as the pivotal phase 3 trial (301), evaluated bleeding/spotting data. Due to differences in the trial design, results are presented separately.

Bleeding/Spotting (B/S) results from Trial 201:
Summary statistics for the total number of bleeding/spotting days during the first two 91-day cycles are shown in Table 24. The percentage of subjects with bleeding/spotting days was similar between all four treatment arms. There was a reduction in the mean total number of B/S days during the second active cycle compared to the first. The median total number of bleeding/spotting days was slightly lower for the low and mid dose arm compared to the Seasonale treatment arm.

Table 24: Study 201: Summary Statistics of Total number of B/S days during each active cycle – ITT Cohort

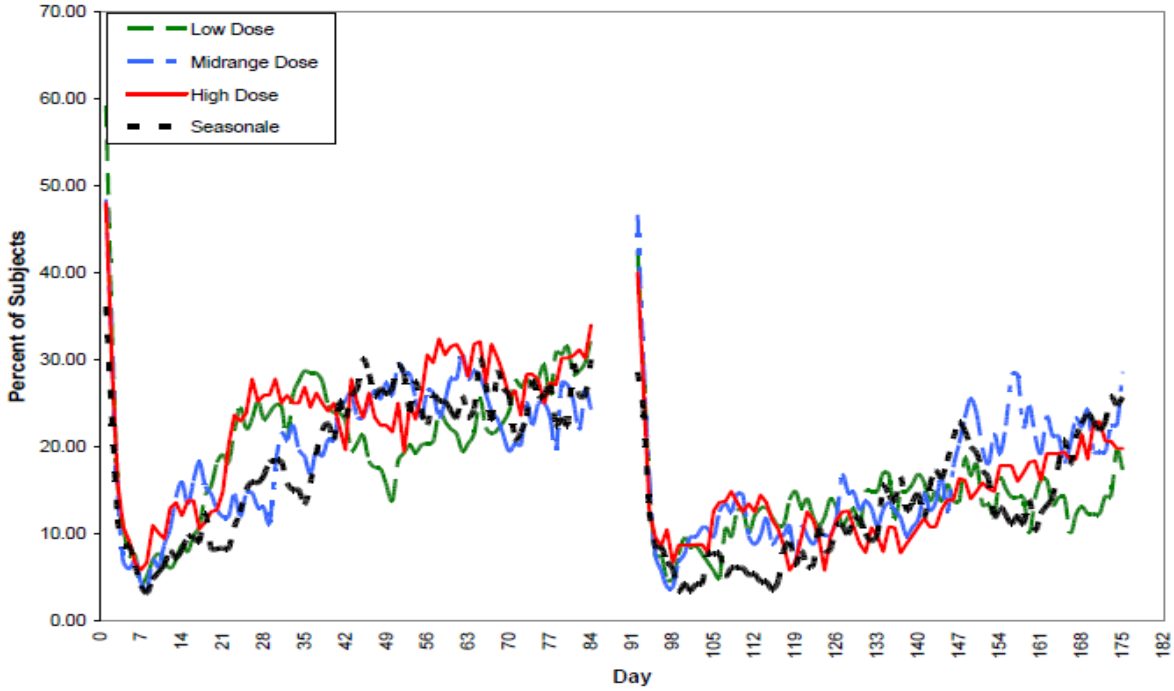
Treatment Groups	Cycle	N	n (%)	Mean (SD)	Min	Median	Max
Low dose	1	110	107 (97.3%)	17.4 (15.59)	0	13	67
	2	109	93 (85.3%)	10.4 (14.15)	0	6	74
Midrange dose	1	110	105 (95.5%)	16.7 (14.81)	0	13.5	65
	2	108	100 (92.6%)	12.2 (13.45)	0	7	70
High dose	1	108	103 (95.4%)	19.5 (16.89)	0	15	69
	2	107	89 (83.2%)	10.9 (14.92)	0	5	74
Seasonale®	1	120	108 (90.0%)	16.4 (13.81)	0	15	56
	2	120	93 (77.5%)	9.8 (11.64)	0	6	55

Note: n (%): Number (percentage) of subjects who experienced any B/S.

Source: Applicant's 201-ectd-body.pdf, pg 56

Figure 1 shows the proportion of subjects with bleeding and spotting events for each treatment over each cycle in Study 201. No difference in the number of events was observed between any of the treatment arms.

Figure 1: Study 201: Proportion of subjects with bleeding or spotting during cycle 1 or 2 over the 84-day active cycle



Source: Applicant's 201-ectd-body.pdf, pg 60

Medical Officer's Comment:
The data do not appear too convincing to support the Applicant's original rationale that this extended-cycle ascending dose product will improve bleeding and/or spotting over the existing marketed products. On the other hand, the bleeding and/or spotting does not look any worse than that observed in the Seasonale arm.

B/S Severity during each active cycle:

B/S Severity was measured on a four-point scale (4=Heavy, 3=Moderate, 2=Light, 1=Spotting and 0=None) as recorded in a daily diary. Table 25 shows average B/S severity during the 28-day run-in period and during each 84-day active cycle in Study 201. Percentage change from run-in to each cycle is based on the difference between the two mean severity scores within each treatment group. All four groups showed a reduction in the mean severity score.

Table 25: Study 201: Average B/S severity scores (scheduled and unscheduled)

Cycle/Status	Quartette	Mid dose	High dose	Seasonale
Run-in	0.53	0.56	0.42	0.43
Active Cycle 1	0.29	0.31	0.34	0.27
Active Cycle 2	0.19	0.22	0.2	0.17
Percentage Change from Run-in				
Active Cycle 1	-45.3%	-44.6%	-19.1%	-37.2%
Active Cycle 2	-64.2%	-60.7%	-52.4%	-60.5%

Source: Table 13, CSR trial 201, page 61.

The analysis of scheduled B/S during each 7-day withdrawal cycle showed that there were no statistically significant differences among the four groups.

Results of bleeding and spotting from trial 301:
The subjects recorded in the daily diaries, subjects were asked to record bleeding or spotting for each day of the week on the scale of 0 (none), 1 (spotting), 2 (light), 3 (moderate), 4 (heavy) where spotting = <1 pads/day, light = 1-2 pads/day, moderate = 3-5 pads/day, heavy = 6+ pads/day.

Medical Officer's Comment:
In the original submission, the Applicant submitted results for total, unscheduled and scheduled bleeding and/or spotting for all subjects who completed at least one complete 91-day cycle of therapy (ITT cohort). This would exclude all women who discontinued the trial due to bleeding/spotting during first 91 days. The Applicant was asked to provide analyses for all subjects who completed at least one 28-day cycle of therapy and also for those who received at least one dose of study drug. Results for all 3 subsets described above were similar. Therefore, results presented here are based on all subjects who completed at least one 28-day cycle of therapy.

Total Days of Bleeding and/or Spotting by Cycle
The total number of days of bleeding and/or spotting by cycle is presented in Table 26 for all treated subjects who completed at least one 28 day cycle.

Table 26: Study 301: Total Number of Bleeding and/or Spotting Days

Cycle	N (All Subjects with at least one complete cycle)	Mean Total Bleeding/ Spotting Days per 91-day cycle	Mean Total Bleeding/ Spotting Days Per 28-day cycle	Median Total Bleeding/ Spotting Days per 91-day cycle	Median Total Bleeding/ Spotting Days Per 28-day cycle
1	3,301	21.1	7.0	17	5.2
2	2,798	12.9	4.3	8	2.5
3	2,425	10.6	3.5	6	1.8
4	2,209	9.7	3.2	6	1.8

Source: Response to IR, date 12/21/2012, Appendix b, page 70

Medical officer's Comment

- ***As seen in* Table 26*, subjects who continue taking the pill had decreased total bleeding and/or spotting over time. This may be partially due to patients with higher rates of bleeding and/or spotting discontinuing the study over time and partially due to an atrophic effect on the endometrium. The sharp decrease from Cycle 1 to Cycle 2 is due at least in part to inclusion of the initial menses at the start of Cycle 1 in the bleeding/spotting calculations for Cycle 1.***
- ***The bleeding/spotting were evaluated after stratification by weight (90 kg and ≥ 90 kg), BMI (< 30 kg/mg^2 and ≥ 30 kg/mg^2), age (< 30 years and ≥ 30 years), smoking (yes and no), and race (Caucasian and other).***
    - ***The results showed that subjects weighing ≥ 90 kg had slightly more bleeding or spotting days compared to subjects weighing < 90 kg (22.7 versus 20.7 total days in cycle 1).***
    - ***The median total number of days of bleeding and/or spotting was about 0.6 day higher per patient-month at Cycle 2 for subjects < 35 years of age compared to those ≥ 35 years of age.***
    - ***These rates were similar regardless of whether a subject had reported a smoking history.***
    - ***The median reported number of days of bleeding and/or spotting was somewhat greater for non-Caucasians; it was 2 days greater at Cycle 2, and one day greater at Cycles 3 and 4.***

Unscheduled Bleeding and/or Spotting by Cycle and Subject Month

The total number of days of unscheduled bleeding and/or spotting by cycle is presented in Table 27 for all treated subjects in the ITT cohort. The information presented in this table is a summary of the daily diary reports from this cohort.

Table 27 Study 301: Unscheduled Bleeding and/or Spotting Days

Cycle	N	Mean Days per 91-day cycle	Mean Per Subject-Month	Median Days per 91-day cycle	Median Per Subject-Month	Minimum/Maximum Days
1	3,300	17.8	4.5	14	3.5	0 / 84
2	2,798	10	2.5	5	1.3	0 / 84
3	2,420	7.7	1.9	3	0.8	0 / 83
4	2,208	6.6	1.7	3	0.8	0 / 66

Source: Response to IR, date 12/21/2012, Appendix B, page 81

Medical Officer's Comments

- ***Unscheduled or unanticipated bleeding and/or spotting (often called "breakthrough" bleeding or spotting) is the most important cycle control parameter to review, as this is the major concern in most patients.***
- ***As shown above in* Table 27*, unscheduled bleeding and/or spotting decreases by the 4th cycle of therapy.***
- ***Although total and unscheduled bleeding and/or spotting can be problematic with extended cycle oral contraceptives, baseline and end of treatment hemoglobin and hematocrit values for subjects taking Quartette do not raise any safety concerns.***

Table 28 below provides cross-study comparisons of unscheduled bleeding and/or spotting per cycle among other approved extended cycle OCs.

Table 28: Mean Unscheduled Bleeding and/or Spotting Days per Subject-Month

Cycle	Seasonale 84 days LNG 150 mcg/EE 30 mcg + 7 days Placebo	Seasonique 84 days LNG 150 mcg/EE 30 mcg + 7 days EE 10 mcg	Lo Seasonique 84 days LNG 100 mcg/EE 20 mcg + 7 days EE 10 mcg	Quartette 84 days LNG 150 mcg/EE 20,25 and 30 mcg + 7 days EE 10 mcg
1	3.8	3.6	4.9	4.5
2	2.9	2.4	3.1	2.5
3	2.7	1.8	2.6	1.9
4	2.2	2.0	2.2	1.7

Source: Seasonale, Seasonique and Lo Seasonique data taken from the Medical Officer reviews of NDA 21-544, NDA 21-840 and 22-262

Medical Reviewer's Comment

Although cross-study comparisons have limitations, it is noted that the bleeding/spotting profile for Quartette is similar to LoSeasonique. This is expected as higher estrogen dose (30 mcg EE) OCs (Seasonale and Seasonique) generally have less unscheduled bleeding than "low dose" OCs such as LoSeasonique and Quartette. Overall, the bleeding profile of Quartette is similar to other extended cycle oral contraceptives.

Scheduled (withdrawal) bleeding and/or spotting:

Summary statistics for the total number of days of scheduled (withdrawal) bleeding and/or spotting during the 7-day period of 10 mcg EE monotherapy (Days 85-91 of the 91-day cycle) are displayed in Table 29.

Table 29: Study 301: Total Number of Scheduled Bleeding and/or Spotting Days per 91-Day Cycle (Complete Cycles Only)

Cycle (91-Day)	N	Mean (SD)		Min	Median	Max
1	2,950	3.7	(2.43)	0	4	8
2	2,497	3.3	(2.40)	0	4	8
3	2,276	3.1	(2.33)	0	3	7
4	2,075	3.3	(2.27)	0	4	7

Source: updated ISS table 48, page 101.

The pattern of scheduled bleeding and/or spotting days was stable across all 4 extended cycles (with the mean number of days ranging from 3.1 to 3.7).

Proportion of Subjects with no Unscheduled Bleeding and/or Spotting Days:

Unscheduled bleeding and/or spotting is reduced after the first and second cycles, and reaches a steady state level beginning with the third cycle, or 6 months following initiation of treatment.

Table 30: Percentage of Subjects with No Unscheduled Days of Bleeding and/or spotting days

Cycle (91-Day)	Subjects	Subjects w/o Bleeding and/or Spotting	%
1	3,064	242	7.9
2	2,615	520	19.9
3	2,361	713	30.2
4	2,170	696	32.1

Source: updated ISS table 59 page 104

Medical Officer's Comment:

- ***The percent of subjects who had any unscheduled bleeding/spotting was > 90% in Cycle 1 and ~70% by Cycle 4. The convenience of extended cycle***

must be balanced against the inconvenience of unscheduled bleeding or spotting.

- ***Slightly higher percents of subjects with baseline body weight < 90 kg did not have unscheduled bleeding and/or spotting at all cycles compared to those with body weight ≥ 90 kg (8.5% vs. 5.2% in cycle 1).***
- ***Higher percentages of subjects ≥ 35 years of age reported no unscheduled bleeding and/or spotting at all cycles compared to those < 35 years of age (10.8% vs. 7.5% in cycle 1).***

7.3.5 Submission Specific Primary Safety Concerns

Pulmonary embolism and deep vein thrombosis were reported in 4 subjects in Study 301; however, one (the PE) occurred in a subject post-treatment with study drug.

Subject 10036-008 ((b) (6)) Bursitis; Pneumonia; DVT

A 28 year-old Hispanic female (BMI 34.6); gravida 4; para 2; and non-smoker, was a continuous user of oral contraceptives (Ovcon-35). Medical history included migraines, therapeutic abortion, laparoscopic ovarian cystectomy, cholecystectomy with appendectomy, pyuria, muscle pain and right hip bursitis. Concomitant medications included Maxalt, Flexeril, naproxen, Percocet, Protonix, Excedrin, multivitamins and fish oil.

The subject began the IP on 07 February 2010. On (b) (6), the subject had right hip heterotopic ossification excision and IT ban lengthening surgery, which was uneventful. She was discharged from the hospital on (b) (6). The subject then developed diaphoresis, shortness of breath, some chest pressure and palpitations and had noted the development of a lacy pruritic rash for the 3-4 days at home. On (b) (6) she presented to the emergency room and was admitted with complaints of chest pain and right arm pain. A Doppler ultrasound demonstrated a right basilic venous and right radial venous thrombosis. CT angiogram of the chest ruled out pulmonary emboli, but, a right upper lobe opacity suggested the presence of atypical pneumonia. Lovenox was initiated and Coumadin was begun on the following day. She was also treated with Rocephin and Zithromax for the atypical pneumonia.

The subject completed the study with her last dose of investigational product on 05 February 2011 and her last visit on 02 March 2011. Her vital signs were stable and the urine pregnancy test result was negative.

Medical Officer's Comment:
This subject had post procedural DVT, which was treated with anticoagulants. The Applicant was asked to explain why a combined hormonal contraceptive in a subject with DVT was not discontinued. On 2/27/13, the Sponsor responded with the following information:
Following review of this serious adverse event, the sponsor contacted the investigator to confirm that the subject had discontinued the IP. The investigator believed that the subject had phlebitis and not DVT or pulmonary embolism and

that it was not related to the IP, but to her recent surgery and subsequent immobility. Following further discussions with the investigator, the sponsor and medical monitor agreed to permit the subject to remain on IP for the remainder of the study, which was 2 weeks, and no additional adverse events or complications were subsequently reported for this subject.

Subject 10069-010 ((b) (6)) DVT

This was a 38 year-old African American female (BMI 41.6); gravida 7; Para 2; elective abortions 5; former smoker, and a prior user of oral contraceptives. Medical history included streptococcal pharyngitis, intermittent migraine headaches with nausea, and Cesarean section.

The subject began the IP on 21 February 2010. She developed cramping in her legs on (b) (6) and chest pain on (b) (6). On (b) (6) she presented to an emergency department with severe pain in both legs. Doppler venous ultrasound showed a left peroneal vein deep venous thrombosis. The study drug was discontinued and the subject was provided with prescriptions for Coumadin 5mg and Lovenox 100 mg. However, the subject could not commence anticoagulant treatment because she was self-funded and could not afford to fill the prescriptions. The subject was discharged the same evening of (b) (6).

The subject did not complete the study, and took her last dose of study drug on (b) (6), and had her final study visit on 10 September 2010. The subject's physical and gynecological examinations, including the Pap smear were normal and the urine pregnancy test result was negative.

Medical Officer's Comment:
The Applicant was asked to explain why the subject was not treated for a serious adverse event. On 2/27/13, the Applicant responded with the following information:
At her end-of-study visit on 10 September 2010, the investigator confirmed that there had been no lapse in medication, that she had completed the full course of enoxaparin. On 09 September 2010, she began warfarin sodium at 5 mg bid, which she was to continue for 6 months.

Subject 10039-037 ((b) (6)) DVT

This was a 29 year-old Caucasian female (BMI 20.1); nulligravida, non-smoker. She was a continuous user of oral contraceptives (YAZ).

The subject began the IP on 13 December 2009. On (b) (6) the subject complained of left lower quadrant pain. Next day she developed swelling of the left lower extremity spreading distally from the thigh, which worsened. She was evaluated in an emergency department on (b) (6). A Doppler ultrasound examination demonstrated extensive deep venous thrombosis including the left iliac, common femoral, and greater saphenous veins with an incidental finding of uterine fibroids. Her last menstrual period was one month prior to admission to the hospital. The subject was treated with Lovenox, Coumadin and graduated compression stockings. Because of the extensive deep vein thrombosis, the oral contraceptive regimen was discontinued.

Her final study visit was 03 February 2010 which her vital signs were stable and the urine pregnancy test result was negative.

Subject 10092-024 ((b) (6)) Pulmonary Embolism

A 32 year-old Caucasian female (BMI 25.7); gravida 1, Para 1; former smoker (2008). She was a continuous user of oral contraceptives (YAZ). Medical history included acne and depression.

The subject began the IP on 13 December 2009. On 4 February 2010 the subject experienced worsening of acne (severe, related to study drug) and discontinued study drug on 13 March 2010 due to this adverse event. The subject restarted YAZ following discontinuation of study drug. On (b) (6) the subject presented to her primary care physician with a 9 day history of chest discomfort with shortness of breath. On (b) (6) subject underwent a computed tomographic angiogram of the chest and was diagnosed with pulmonary embolism. A genetic analysis demonstrated that the subject was negative for the factor V Leiden mutation. Subject received subcutaneous Lovenox 120 mg daily and warfarin 2.5-7.5 mg daily. The Investigator deemed the event related to study drug. The subject discontinued the study due to an adverse event and took her last dose of study drug on 13 March 2010 and had her last study visit on 9 April 2010 in which her vital signs were stable and the urine pregnancy test results was negative.

Medical Officer's Comment:
This event occurred on YAZ, not on IP. This means 3 subjects out of 3,700 experienced a DVT. This incidence is similar to other contraceptives (3-9/10,000 women years).

Anaphylactic reactions:
Analysis of the updated ISS datasets showed 6 subjects identified using the algorithmic SMQ "Anaphylactic reaction." The Applicant was asked to provide detailed information on these subjects' adverse events.

Unique Subject ID	Adverse events
AL-0021-10021003	cough, rash, sneezing
CA-0028-10028007	cough, pruritus, urticaria
NJ-0003-10003019	cough, rash,
NY-0026-10026012	urticaria, cough
WA-0053-10053031	cough, flushing
WA-0053-10053091	cough, urticaria

Source: Medical Officer's analysis of Adverse Event dataset, ISS using MAED and Jreview programs.

The Applicant responded and provided their assessment as to whether these events constituted hypersensitivity reactions or anaphylactic reactions. Five of the six subjects had medical histories that included various respiratory or allergic disorders; the principal investigator attributed the adverse events of cough, sneezing, rash, pruritus, and urticaria experienced by these 5 subjects to the recurrence of their preexisting respiratory or allergic conditions. For the subject CA-0028-10028007, who did not have

a medical history of preexisting respiratory or allergic conditions, the principal investigator attributed the adverse events of cough, urticaria, and pruritus to causes other than the IP because of the subject's medication history, timing of the onset of each adverse event in relation to IP treatment dates, and general clinical presentation. IP was not discontinued for any of these subjects due to any of these adverse events. Upon review of details provided by the Applicant, I agree with the Applicant's assessment that above-mentioned adverse events were not related to anaphylactic reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 31 shows the incidence rates for the most frequently reported treatment-emergent adverse events by system organ class for the Safety Cohort. The three most common system organ classes were Infections and Infestations, Reproductive System Disorders and Gastrointestinal Disorders.

Table 31: Common Adverse Events (> 5% of subjects) in the ISS safety population by system organ class

	Quartette (N = 3737)		
SOC	Events	Number of subjects	%
Infections and infestations	3,110	1,671	44.7
Reproductive system and breast disorders	1,344	858	23.0
Gastrointestinal disorders	1,087	676	18.1
Nervous system disorders	1,139	599	16.0
Musculoskeletal and connective tissue disorders	648	408	10.9
Psychiatric disorders	542	403	10.8
Respiratory, thoracic and mediastinal disorders	529	381	10.2
Skin and subcutaneous tissue disorders	442	363	9.7
Investigations	390	326	8.7
General disorders and administration site conditions	319	276	7.4
Injury, poisoning and procedural complications	315	264	7.1

Source: Medical Officer's analysis of ISS Adverse Event dataset using MAED program

Table 32 shows the incidence rates for the most frequently reported treatment-emergent adverse events (incidence rates of 2% or greater) for the Safety Cohort.

Table 32: Common Adverse Events (≥ 2%), occurring in Quartette vs. Seasonale

	Quartette (N = 3737)			Seasonale (N = 148)		
PT	**Events**	**n**	**%**	**Events**	**N**	**%**
Headache	**863**	**457**	**12.2**	**48**	**26**	**17.6**
Nasopharyngitis	498	395	10.6	18	12	8.1
Upper respiratory tract infection	459	368	9.9	10	10	6.8
Sinusitis	332	270	7.2	10	10	6.8
Nausea	**304**	**250**	**6.7**	**8**	**8**	**5.4**
Urinary tract infection	290	247	6.6	2	2	1.4
Metrorrhagia	**331**	**219**	**5.9**	**6**	**4**	**2.7**
Dysmenorrhoea	**283**	**212**	**5.7**	**11**	**8**	**5.4**
Acne	**218**	**195**	**5.2**	**3**	**3**	**2.0**
Weight increased	**182**	**176**	**4.7**	**9**	**9**	**6.1**
Back pain	212	168	4.5	8	7	4.7
Vulvovaginal mycotic infection	**171**	**149**	**4.0**	**3**	**1**	**0.7**
Cervical dysplasia	157	146	3.9	0	0	0.0
Vaginitis bacterial	**161**	**144**	**3.9**	**9**	**9**	**6.1**
Bronchitis	123	116	3.1	2	2	1.4
Vaginal haemorrhage	**179**	**114**	**3.1**	**2**	**2**	**1.4**
Cough	107	103	2.8	5	5	3.4
Sinus congestion	115	94	2.5	3	3	2.0
Depression	**99**	**93**	**2.5**	**7**	**7**	**4.7**
Fungal infection	110	89	2.4	6	3	2.0
Pharyngitis streptococcal	94	89	2.4	2	2	1.4
Anxiety	**92**	**87**	**2.3**	**6**	**5**	**3.4**
Oropharyngeal pain	93	83	2.2	0	0	0.0
Abdominal pain	96	80	2.1	1	1	0.7
Breast tenderness	**82**	**76**	**2.0**	**0**	**0**	**0.0**
Gastroenteritis viral	83	76	2.0	1	1	0.7
Vomiting	**90**	**76**	**2.0**	**2**	**2**	**1.4**
Influenza	78	75	2.0	5	5	3.4

Medical Officer analysis using MAED program.

Medical Officer's Comment:
The most common drug-related adverse events (relationship to treatment assessed by this reviewer) for this product with rates ≥ 2.0% were headache (12.2%), vaginal bleeding or metrorrhagia (9%) nausea (6.7%), dysmenorrhea (5.7%), acne (5.2%), increased weight (4.7%), vulvovaginal mycotic infection (4%), bacterial vaginitis (3.9 %), acne (3.2%), depression (2.5%), anxiety (2.3%), vomiting (2%), and breast tenderness (2%).

7.4.2 Laboratory Findings

Chemistry: For total cholesterol, the to-be-marketed dose was associated with a median reduction of 10 mg/dL compared to a 7.0 mg/dL median increase for the midrange dose and a 6.0 mg/dL median increase for the high dose. For HDL, the to-be-marketed dose provided a 5 mg/dL median reduction from baseline to endpoint, LDL increased by a median of 13 mg/dL and triglycerides increased by a median of 1.0 mg/dL for the subjects treated with the to-be-marketed dose. For glucose, median change from baseline (88 mg/dl) was -2mg/dl in the to-be-marketed dose group.

Shift tables:
For total cholesterol, 8% (172/2128) of to-be-marketed dose subjects who were within the normal range at baseline were above the upper limit of normal at the end of study. A total of 3% (56/2128) subjects on the to-be-marketed dose who were within the normal range at baseline shifted from normal to low .

For HDL, no subjects in any treatment group shifted from normal at baseline to high at endpoint. A total of 3% (100/2975) of to-be-marketed dose subjects shifted from normal to low compared to 0% (0/112) of midrange and 2% (2/125) of high dose subjects.

Shifts in LDL to high at endpoint were observed in 23% (588/2555) of to-be-marketed dose subjects who were normal at baseline.

For triglycerides, 3% (69/2553) to-be-marketed dose subjects who were normal at baseline shifted to above the upper limit of normal at endpoint. Subjects who were normal at baseline but then shifted to below the lower limit of normal at endpoint included 7% (177/2553) of to-be-marketed dose subjects.

Table 33: Shift tables for lipid profile in the ISS safety dataset

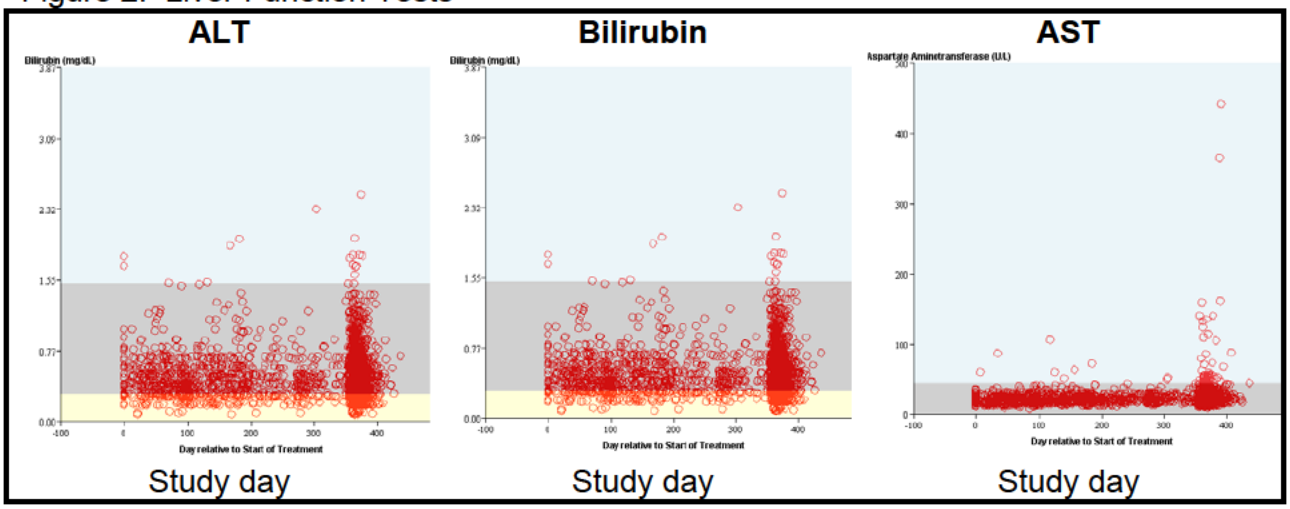
N=3737	Baseline low	Baseline normal	Baseline high
Total Cholesterol (mg/dL)			
End point Low	17	56	1
End point Normal	17	1900	450
End point High	1	172	434
HDL			
End point Low	40	100	0
End point Normal	33	2875	0
End point High	0	0	0
LDL (mg/dL)			
End point Low	0	0	0
End point Normal	0	1967	87
End point High	0	588	406
Triglycerides (mg/dL)			
End point Low	131	177	1
End point Normal	268	2307	62
End point High	0	69	33
Glucose (mg/dL)			
End point Low	0	17	0
End point Normal	5	2521	217
End point High	0	176	75

Source: updated ISS table 13, page 55

Hematology: Median change from baseline to end of study for platelet counts (nL), of +4 was observed for the to-be-marketed dose group compared to an median decrease of 5.5 for subjects in the midrange group and a median decrease of 5 in the high dose group. Other hematologic parameters did not show any significant change from baseline.

Liver Function Test: There were 9 subjects with elevations in liver function tests, shown in Figure 2 below.

Figure 2: Liver Function Tests



Medical Officer's Comment:
While abnormalities of liver function tests were observed, none of these cases met Hy's law criteria of AST or ALT > 3 times normal and >2 times normal bilirubin.

Table 34: Subjects with AST, ALT >3 times normal or bilirubin >2 times normal in Trial 301

Subject ID	Lab test	Result	unit	Upper limit of normal	Date and time
FL-0034-10034022	AST	156	U/L	45	2009-10-12
FL-0013-10013043	AST	165	U/L	45	2010-05-13
CO-0004-10004014	ALT	182	U/L	55	2011-01-06
FL-0029-10029051	AST	365	U/L	45	2011-04-25
FL-0088-10088008	ALT	524	U/L	55	2010-03-15
FL-0088-10088008	ALT	257	U/L	55	2010-03-01
FL-0088-10088008	AST	166	U/L	45	2010-03-15
GA-0010-10010019	ALT	203	U/L	55	2010-12-10

Source: Medical Officer's analysis of LB dataset using JMP program
ALT = Alanine transaminase; AST = aspartate transaminase; bili= Bilirubin

Subjects 10013043 and 10034022 had elevated AST values at screening, but, on repeat testing, all laboratory test results, including AST, were within the normal range. Liver function test (LFT) results for both subjects were within the normal range at the final study visit. The remaining 4 subjects (subjects 10004014, 10010019, 10029051, and 10088008) had normal LFT results at screening, were enrolled into the study, and took IP for 1 month to 1 year. At the final study visit (early withdrawal or study completion), each of these subjects had elevations in either ALT or AST values or both.

Subject 10004014 was referred to her primary care physician for further evaluation. The remaining 3 subjects were monitored by the investigator until the abnormalities resolved—as defined either by the values returning to within the normal range or by the investigator no longer considering the values clinically significant. For subject 10029051, elevated liver enzymes were attributed to an herbal supplement she had begun taking. For the remaining 3 subjects, the investigator had no definitive explanation for the transient increases in the ALT and AST values.

Medical Officer's Comment:
It is not unexpected to see a few subjects with increase in LFT in a clinical trial of >3700 subjects. No new safety signal is found upon evaluation of this data.

7.4.3 Vital Signs

Vital signs were recorded for each subject at the baseline visit and at each visit The Applicant presented change from baseline data for those subjects who had baseline data and data at the endpoint visit.

There were no safety concerns related to vital signs or body weight in the pivotal phase 3 trial.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in the pivotal phase 3 trial and are not required for this well-characterized combination drug product.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no dose-dependent safety findings, as only a single dose was studied in the phase 3 trial.

7.5.2 Time Dependency for Adverse Events

There were no significant time-dependent safety findings.

7.5.3 Drug-Demographic Interactions

The drug-demographic interactions with BMI were discussed in Section 6.1.7.

7.5.4 Drug-Disease Interactions

There was no disease studied in the trials for this product (contraceptive study in healthy women).

7.5.5 Drug-Drug Interactions

No assessment of drug-drug interactions was undertaken for either Study 201 or 301. As EE and LNG are well studied drugs and the doses of this product fall within the range of other approved NDAs, this is acceptable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See Section 4.3 and the preclinical review.

7.6.2 Human Reproduction and Pregnancy Data

See Section 4.3 and the preclinical review

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric Waiver Request:

The Pediatric Review Committee (PeRC) agreed to the Applicant's requested partial waiver/extrapolation of adult data to post-menarchal adolescents. Use of COCs before menarche is not indicated. According to the class labeling for COCs, the safety and efficacy of LNG and EE tablets and EE tablets have been established in women of reproductive age, and are expected to be the same for post-pubertal adolescents under the age of 18 as for users 18 years and older.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant did not have any reports of deleterious effect from overdose. Symptoms that would probably occur with overdose include nausea and possibly abnormal uterine bleeding. The drug abuse potential for COCs is very low. The primary withdrawal effect is physiologic withdrawal bleeding.

7.7 Additional Submissions / Safety Issues

The 4-Month Safety Update was received 9/27/2012. This safety update contained new information for 5 subjects who were enrolled in Study 301 (4 subjects with pregnancies and 1 subject with a pregnancy and serious adverse event) obtained after the study database was locked. The review of this safety update did not provide any information that would impact the approval of this product or labeling of this product.

8 Postmarket Experience

There is no postmarketing experience with this dosage and sequence of EE and LNG. There is extensive postmarketing experience with higher and lower dosage combinations. The Division has not received any new significant safety information from these other EE/LNG products that would impact the approval of this application.

9 Appendices

9.2 Labeling Recommendations

This reviewer's recommendations regarding labeling include the following key points:

- The clinical section of the label should report a Pearl Index based on 70 pregnancies (PI = 3.19) rather than 65.
- The bleeding/spotting data tables should be revised as shown in the labeling document.
- Please refer to the labeling document for details.

9.3 Advisory Committee Meeting

An advisory committee meeting was not required. The combination products (EE and LNG) are well-characterized in regard to efficacy and safety and have been marketed for over 40 years.

Table 35: Detailed pregnancy table for Trial 301

#	Subject ID	Age	Treatment start date	Treatment stop date	Ultrasound Date	Conception date	PITT	On-drug per Applicant	On-drug per FDA Comment
'on-drug' Pregnancy in PITT population									
1	FL-0001-10001115	28	10-07-25	10-10-23	10-11-30	10-10-30	Y	N	Y within 7 days of last pill
2	NC-0042-10042029	24	09-11-29	10-01-19	10-03-18	10-01-26	Y	N	Y within 7 days of last pill
3	MD-0005-10005055	19	10-05-02	11-03-22			Y		Y pregnancy not confirmed by the Applicant as subject lost to follow-up.
4	AR-0062-10062057	27	10-06-20	11-06-18	11-08-05	11-06-18	Y	N	Y within 7 days of last pill
5	GA-0010-10010058	25	10-06-20	11-06-18	11-07-20	11-06-22	Y	N	Y within 7 days of last pill
6	AZ-0059-10059011	27	10-04-05	11-03-27			Y	Y	Y
7	CA-0028-10028050	30	10-05-02	10-08-15	10-08-16	10-07-29	Y	Y	Y
8	CA-0052-10052033	25	09-12-20	10-12-16			Y	Y	Y
9	CA-0052-10052065	19	10-03-14	10-08-15	10-08-16	10-08-02	Y	Y	Y
10	CA-0052-10052090	34	10-05-23	11-05-19			Y	Y	Y
11	CA-0052-10052105	23	10-06-13	10-10-28	10-10-29		Y	Y	Y
12	CA-0075-10075011	24	09-12-06	10-03-03	10-03-22	10-02-22	Y	Y	Y
13	CA-0075-10075020	31	09-12-27	10-02-19	10-02-22	10-01-28	Y	Y	Y
14	CA-0075-10075048	30	10-04-25	11-01-16	11-01-21	10-12-28	Y	Y	Y
15	CA-0098-10098049	29	10-04-11	10-11-29	10-12-03	10-10-29	Y	Y	Y
16	CA-0098-10098053	25	10-04-25	10-09-03	10-10-08	10-08-15	Y	Y	Y
17	DC-0082-10082003	27	09-11-29	10-04-05	10-04-06	10-02-15	Y	Y	Y
18	FL-0001-10001072	24	10-04-25	10-10-27	10-11-03	10-10-13	Y	Y	Y
19	FL-0001-10001078	24	10-04-11	10-12-27	11-01-03	10-12-03	Y	Y	Y

#	Subject ID	Age	Treatment start date	Treatment stop date	Ultrasound Date	Conception date	PITT	On-drug per Applicant	On-drug per FDA Comment
20	FL-0029-10029059	30	10-06-06	11-05-13	11-05-23	11-03-14	Y	Y	Y
21	FL-0034-10034240	27	10-07-25	10-10-18	10-10-25	10-09-27	Y	Y	Y
22	FL-0056-10056007	23	09-12-20	10-03-16			Y	Y	Y
23	FL-0056-10056036	21	09-12-27	10-05-03	10-05-06	10-04-19	Y	Y	Y
24	FL-0067-10067119	28	10-06-13	10-08-05	10-08-05		Y	Y	Y
25	GA-0010-10010015	25	09-12-13	10-02-08	10-01-22	09-12-26	Y	Y	Y
26	GA-0010-10010035	28	10-02-28	11-02-18	11-03-01	10-11-23	Y	Y	Y
27	KS-0051-10051048	24	10-02-21	10-08-14	10-08-16	10-07-20	Y	Y	Y
28	KS-0051-10051083	33	10-05-09	10-11-23	10-12-13	10-11-21	Y	Y	Y
29	KS-0051-10051102	20	10-07-25	11-06-07	11-07-11	11-05-25	Y	Y	Y
30	KY-0022-10022053	23	10-05-30	10-08-22			Y	Y	Y
31	KY-0022-10022074	24	10-07-18	10-11-26	10-12-01	10-10-15	Y	Y	Y
32	KY-0049-10049020	20	10-05-30	10-10-30	10-11-08	10-10-15	Y	Y	Y
33	LA-0044-10044006	27	10-01-17	10-04-12	10-04-12	10-03-26	Y	Y	Y
34	MO-0089-10089004	21	10-07-11	11-03-12	11-03-28	11-02-26	Y	Y	Y
35	NC-0042-10042009	27	09-11-08	10-06-24	10-07-07	10-06-04	Y	Y	Y
36	NC-0042-10042035	23	09-12-13	10-08-03	10-08-10	10-07-20	Y	Y	Y
37	NC-0060-10060008	18	09-12-06	10-05-14			Y	Y	Y
38	NC-0065-10065006	18	09-11-22	10-05-17	10-05-28	10-04-23	Y	Y	Y
39	NC-0065-10065022	24	10-01-31	10-12-14	10-12-24	10-11-22	Y	Y	Y
40	NC-0065-10065024	21	10-02-07	10-11-03	10-11-09	10-10-13	Y	Y	Y
41	NC-0065-10065045	24	10-05-16	10-06-10	10-06-17		Y	Y	Y
42	NC-0065-10065057	21	10-06-20	11-04-24	11-05-04	11-03-21	Y	Y	Y
43	NC-0073-10073012	25	09-12-20	10-02-09			Y	Y	Y
44	NC-0073-10073018	28	09-12-20	10-12-15	11-01-28	10-11-01	Y	Y	Y
45	NC-0073-10073046	22	10-03-14	11-02-05			Y	Y	Y
46	NC-0077-10077040	29	10-02-21	10-05-20			Y	Y	Y
47	NC-0077-10077051	29	10-06-20	10-09-14	10-10-27	10-09-12	Y	Y	Y
48	NC-0087-10087053	31	10-06-20	10-08-30	10-09-07	10-08-15	Y	Y	Y

#	Subject ID	Age	Treatment start date	Treatment stop date	Ultrasound Date	Conception date	PITT	On-drug per Applicant	On-drug per FDA Comment
49	NJ-0058-10058007	29	09-12-06	10-07-31			Y	Y	Y
50	NJ-0058-10058030	27	10-03-07	10-10-08	10-10-26		Y	Y	Y
51	NV-0007-10007004	28	09-11-15	10-09-21	10-10-29	10-09-08	Y	Y	Y
52	NV-0007-10007014	18	10-01-10	10-03-01	10-04-12	10-02-11	Y	Y	Y
53	NY-0026-10026008	30	09-11-15	10-07-18	10-08-03	10-06-27	Y	Y	Y
54	NY-0026-10026034	30	10-02-07	10-07-10	10-08-17	10-06-30	Y	Y	Y
55	OH-0071-10071042	30	09-12-20	10-01-14	10-01-25	09-12-27	Y	Y	Y
56	OH-0071-10071065	19	10-02-14	10-08-10	10-09-13	10-08-16	Y	Y	Y
57	PA-0080-10080121	20	10-04-04	11-03-13	11-03-18	11-02-02	Y	Y	Y
58	PA-0080-10080148	19	10-05-30	11-01-24	11-01-24	10-12-05	Y	Y	Y
59	PA-0080-10080150	20	10-05-30	11-02-19	11-02-28	11-01-20	Y	Y	Y
60	SC-0090-10090037	23	10-02-07	10-07-11	10-07-21	10-06-28	Y	Y	Y
61	TN-0072-10072044	23	10-03-28	10-12-06			Y	Y	Y
62	TN-0072-10072048	27	10-04-25	10-09-02	10-09-09	10-08-08	Y	Y	Y
63	TN-0084-10084015	34	10-01-24	10-07-18	10-07-20	10-06-21	Y	Y	Y
64	TX-0002-10002015	30	09-12-13	10-01-05		09-12-22	Y	Y	Y
65	TX-0002-10002029	24	10-02-14	10-07-28			Y	Y	Y
66	TX-0014-10014016	19	10-03-07	10-05-31	10-06-01	10-05-19	Y	Y	Y
67	TX-0014-10014023	28	10-05-02	11-04-25	11-05-16	11-02-25	Y	Y	Y
68	TX-0041-10041029	18	10-01-03	10-02-16	10-02-19		Y	Y	Y
69	VA-0040-10040012	30	10-07-11	11-02-04	11-02-23	11-01-22	Y	Y	Y
70	VA-0050-10050017	21	10-03-21	10-08-16	10-08-19	10-07-21	Y	Y	Y
Off-drug pregnancy in PITT population									
71	NC-0065-10065038	21	10-04-25	11-04-16		2010-04-29	Y	N	N Applicant's conception date is based on β-HCG level.
72	FL-0056-10056005	28	09-12-20	10-02-01		10-03-13	Y	N	N
73	CA-0052-10052014	32	09-12-27	10-02-19	10-02-22	09-11-25	Y	N	N

#	Subject ID	Age	Treatment start date	Treatment stop date	Ultrasound Date	Conception date	PITT	On-drug per Applicant	On-drug per FDA Comment
74	CA-0075-10075006	22	09-11-15	10-11-13	10-12-08	10-11-24	Y	N	N
75	NC-0065-10065031	18	10-03-28	10-09-19	10-12-01	10-11-07	Y	N	N
76	NE-0092-10092015	26	10-01-10	10-04-03	10-09-14	10-07-22	Y	N	N
77	TN-0035-10035023	29	09-12-20	10-04-28	10-09-20	10-06-23	Y	N	N
Pregnancies in Non-PITT population									
78	NC-0009-10009024	23	10-01-24	10-02-07	10-03-19	10-02-25	N	N	N
79	NY-0018-10018040	19	10-02-07	10-02-07		10-01-18	N	N	N
80	TN-0072-10072002	22	09-11-08	09-11-08	09-12-09	09-10-26	N	N	N
81	TX-0079-10079029	38	10-02-21	10-08-14	10-12-14	10-10-13	N	N	Y The date of discontinuation of IP was unknown. On 8/11/2010 the subject called the study site to report pregnancy.

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

/s/

VAISHALI B POPAT
03/01/2013

LISA M SOULE
03/01/2013
I concur with Dr. Popat's conclusions and recommendation that NDA 204-061 be approved for prevention of pregnancy.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Final
(July 26, 2012)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204061	Brand Name	Quartette™
OCP Division (I, II, III, IV, V)	III	Generic Name	Levonorgestrel (LNG)/ ethinyl estradiol (EE)
Medical Division	DRUP	Drug Class	Hormonal Oral Contraceptive
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication	Prevention of Pregnancy
OCP Secondary Reviewer/Signer	Myong-Jin Kim, Pharm.D.	Dosage Form	0.15/0.02, 0.15/0.025, and 0.15/0.03 mg LNG/EE, and 0.010 mg EE
Pharmacometrics Reviewer	Jeff Florian, Ph.D.	Dosing Regimen	QD for 91 days
Date of Submission	May 31, 2012 (cover letter)	Route of Administration	Oral
Estimated Due Date of OCP Review	December 2012	Sponsor	Teva Branded Pharmaceutical Products, Frazer, PA
Medical Division Due Date	January 2013	Priority Classification	Standard
PDUFA Due Date	March 31, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE		**X**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table of Contents present and sufficient to locate reports, tables, data, etc.		**X**		
Tabular Listing of All Human Studies		**X**		
HPK Summary		**X**		
Labeling		**X**		
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology	**X**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		In addition, cross reference three NDAs for PK data: NDA 021544 for Seasonale, 021840 for Seasonique, and 022262 for LoSeasonique**.**
Healthy Volunteers-				
single dose:	**X**	1		
multiple dose:	**X**	1		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

hepatic impairment:				
PD -				
Phase 2:	**X**	**1**		
Phase 3:	**X**	**1**		
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**1**		New PK data from DR-103-101 (n=18). Other PK from previous NDA submissions (021544, 021840, and 022262
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	x	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
***In vitro* Penetration Studies**				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to			X	waiver and

	demonstrate effectiveness, if the drug is indeed effective?				deferral requests
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_

Executive Filing Summary:

What is the reason for this type of regimen?

This is original NDA for 91 days regimen and new strengths of the approved formulations and Combination Oral Contraceptive-COC (Seasonale NDA 021544, Seasonique NDA 021840, and LoSeasonique NDA 022262). The proposed trade name of the product is Quarette™ also known as DR-103. The product (i.e., the package) will consist of two sets of tablets. One set contains a combination of levonorgestrel-LNG/ethinyl estradiol-EE in ascending strengths for EE and a fixed strength for LNG for 84 days regimen and a second set contains EE alone for 7 days regimen (total regimen is 91 days). The tablets will be identified by four different colors as follows:

A: 42 light pink tablets containing 150 mcg LNG and 20 mcg of EE
B: 21 pink tablets containing 150 mcg of LNG and 25 mcg of EE.
C: 21 purple tablets containing 150 mcg of LNG and 30 mcg of EE.
D: 7 yellow tablets containing 10 mcg of EE only.

From the clinical pharmacology perspective and as mentioned above the sponsor crossed referenced three products and manufactured by the same technology and manufacturing site (**Table 1**). Therefore, from the PK perspective, the sponsor conducted only one PK study to investigate the relative bioavailability of the three tablet strengths following a single dose and at steady state (Study DR-103-101, also known as (b) (4) study 10936010, **Table 2**). Furthermore, the sponsor performed Pop PK analysis of the data.

Table 1: Studies Included in the Analyses Discussed in The Summary of Clinical Pharmacology Studies

		Study ID (number of subjects)	
Product	**Dosage regimen**	**Characterization of pharmacokinetics[a]**	**Characterization of PK/PD relationships**
DR-103	days 1 through 42: LNG 150 mcg/ EE 20 mcg days 43 through 63: LNG 150 mcg/ EE 25 mcg days 64 through 84: LNG 150 mcg/ EE 30 mcg days 85 through 91: EE 10 mcg	DR-103-101 (also referred to as (b) (4) study 10936010) (n=18)	DR-103-301 (n=2972)
Seasonale	days 1 through 84: LNG 150 mcg/ EE 30 mcg days 85 through 91: placebo	99028 (n=29)	NA
Seasonique	days 1 through 84: LNG 150 mcg/ EE 30 mcg days 85 through 91: EE 10 mcg	10216207 (n=30) 10416204 (n=29) R00-570 (n=17)	DR-PSE-301 (n=708)
LoSeasonique	days 1 through 84: LNG 100 mcg EE 20 mcg days 85 through 91: EE 10 mcg	99027 (n=30)	DR-PSE-309 (n=1950)

[a]All studies assessed single-dose pharmacokinetics. Seasonique study 10216207 also assessed multiple-dose pharmacokinetics.
LNG=levonorgestrel; EE=ethinyl estradiol; ID=identification; PK=pharmacokinetic; PD=pharmacodynamic; NA=not applicable.

Table 2. PK Study (DR-103-101)

Study number Study title (design) Phase	No. of centers Location	Status Dates	Study population Variables	Dose regimen Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg): mean (range)
Biopharmaceutic Studies: Bioavailability (BA) Studies						
10936010 A Study to Evaluate the Relative Bioavailability of Three Different Dosage Strengths of a New Ethinyl Estradiol/Levonorgestrel Contraceptive, DR-103 (Teva Pharmaceuticals USA), Following a Single Oral Dose in Healthy Females Under Fasted Conditions Phase 1	1 center USA	Completed 20 Oct 09-19 Dec 09	Healthy, non-tobacco using adult women Relative bioavailability: C_{max} t_{max} AUC_{0-t} AUC_{0-inf} Ct Kel Ct/Kel $t_{½}$ Safety: AEs clinical laboratory test results (hematology and clinical chemistry) vital signs measurements physical examination findings (including gynecologic examination) ECGs	LNG/EE tablets (DR-103) (administration following overnight fasting of at least 10 hours): Period 1: 2 x 0.15 mg LNG/0.02 mg EE tablets, taken orally Period 2: 2 x 0.15 mg LNG/0.025 mg EE tablets, taken orally Period 3: 2 x 0.15 mg LNG/0.03 mg EE tablets, taken orally 9 weeks	LNG/EE tablets (DR-103): 0.15 mg LNG/0.02 mg EE tablets (mfg batch: 210030, pkg batch: 220095) 0.15 mg LNG/0.025 mg EE tablets (mfg batch: 210029, pkg batch: 220093) 0.15 mg LNG/0.03 mg EE tablets (mfg batch: 210028, pkg batch: 220092)	N=18 Subjects below were included in the statistical analysis set: Period 1: N=17 26.65 (19-39) 0/17 (0/100) 0/11/6 (0/64.71/35.29) 151.76 (106-195) (weight in lbs) Period 2: N=17 26.65 (19-39) 0/17 (0/100) 0/11/6 (0/64.71/35.29) 151.76 (106-195) (weight in lbs) Period 3: N=16 26 (19-39) 0/16 (0/100) 0/10/6 (0/62.5/37.5) 150.13 (106-195) (weight in lbs)

In addition to the PK study, the sponsor conducted one Phase 2 study to determine the bleeding patterns (Study Study # DR-ASC-201, **Table 3**) and one Phase III safety and efficacy study (DR-103-301, **Table 4**).

Table 3 (Bleeding Patterns, Phase 2 Study DR-ASC-201)

Study number Study title (design) Phase	No. of centers Location	Status Dates	Study population Variables	Dose regimen Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg): mean (range)
Human Pharmacodynamic (PD) Studies: Healthy Subject Pharmacodynamic Studies						
DR-ASC-201 A Prospective, Multicenter, Double-Blinded, Randomized Study to Evaluate Bleeding Patterns in Women Using One of Three Different Ascending EE Dose Extended Cycle (91-Day) Oral Contraceptive Regimens (DR-1031) Compared to Seasonale® Oral Contraceptive Regimen Phase 2	51 centers USA	Completed 27 Oct 06-04 Mar 08	Healthy women Primary efficacy: total bleeding and/or spotting days during active treatment Secondary efficacy: total bleeding days during active treatment periods time to first bleeding maximum bleeding severity scheduled withdrawal bleeding (onset, duration, and severity) proportion of women reporting hormone-related symptoms (including breast tenderness/pain, headache, bloating, pelvic pain, anxiety, depression, and irritability) during active treatment and withdrawal periods Safety: AEs clinical laboratory test results (hematology, blood chemistry, and urinalysis) vital signs measurements physical and gynecologic examination results	Eligible subjects receive a 28-day run-in cycle of Portia® taken orally (21 days of 30 mcg EE/150 mcg LNG followed by 7 days of placebo) Subjects were randomly assigned to 1 of the following OC treatment groups (investigational product in groups 1, 2, and 3 was administered for 2 consecutive 91-day extended cycles): Group 1 (low dose) (DR-103): 42 days of 20 mcg EE/150 mcg LNG, 21 days of 25 mcg EE/150 mcg LNG, 21 days of 30 mcg EE/150 mcg LNG, followed by 7 days of 10 mcg EE Group 2 (midrange dose) (DR-103): 21 days of 20 mcg EE/150 mcg LNG, 42 days of 25 mcg EE/150 mcg LNG, 21 days of 30 mcg EE/150 mcg LNG, followed by 7 days of 10 mcg EE Group 3 (high dose): 21 days of 20 mcg EE/150 mcg LNG, 21 days of 25 mcg EE/150 mcg LNG, 42 days of 30 mcg EE/150 mcg LNG, followed by 7 days of 10 mcg EE Group 4 (Seasonale®): 84 days of 30 mcg EE and 150 mcg LNG, then 7 days of placebo for 2 consecutive 91-day cycles Approximately 9 months	LNG/EE tablets (DR-103): Low-dose tablets ($00081 and 210013) Midrange tablets ($00080 and 210012) High-dose tablets ($00079 and 210011) Portia tablets (301430 and 302271) Seasonale tablets ($00077 and 210010)	N=567 (subjects treated with at least 1 dose of randomized study drug) N=448 (subjects treated for at least 1 treatment cycle) 30.5 (18.2, 45.8) 0/448 (0/100) 291/150/7 (65/33.4/1.6) 154.4 (94.0-244.0) (weight in lbs)

Table 4 (Phase III Study DR-ASC-201)

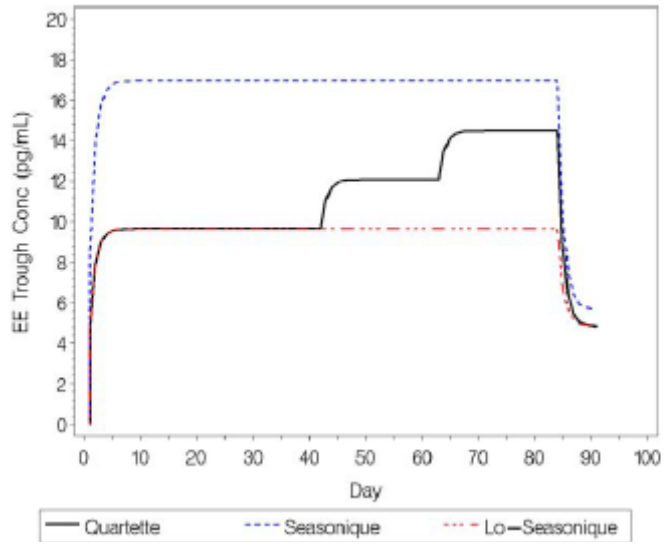
Study number Study title (design) Phase	No. of centers Location	Status Dates	Study population Variables	Dose regimen Duration of treatment	Formulation (Batch/Lot no.)	No. treated Age (yr): mean (range) M/F (%) W/NW/U (%) Weight (kg): mean (range)
Efficacy and Safety Studies: Clinical Studies Pertinent to the Claimed Indication						
DR 103-301 A Multicenter, Open-label Study to Evaluate the Efficacy and Safety of a Combination Oral Contraceptive Regimen (DR-103) for the Prevention of Pregnancy in Women Phase 3	98 centers USA	Completed 08 Oct 09-09 Sep 11	Healthy, sexually active women who were at risk of pregnancy Primary efficacy: Pearl index using all pregnancies (all-users pregnancy rate, typical-use pregnancy rate, and compliant-use pregnancy rate) Secondary efficacy: life table analysis using cumulative pregnancy rates Safety: AEs concomitant medication usage clinical laboratory test results vital signs measurements reports of bleeding and spotting in daily diary	LNG/EE tablets (DR-103) OC regimen utilizing ascending EE doses: 42 days of 20 mcg EE/150 mcg LNG, 21 days of 25 mcg EE/150 mcg LNG, 21 days of 30 mcg EE/150 mcg LNG, followed by 7 days of 10 mcg EE 1 year	LNG/EE tablets (DR-103): (0001020361, 0001025677, 220085, and 220086)	N=3597 27.1 (18-41) 0/3597 (0/100) 2324/1202/71 (65/33/2) 162.5 (83-402) (weight in lbs)

Reviewer's Comments:

The PK of LNG and EE is well characterized in other products and in the literature. From the clinical pharmacology perspective, the sponsor's proposed label contains the same information in reference to absorption, distribution, metabolism and excretion as that of other class products and primarily Seasonique and LoSeasonique. Similarly, the information related to drug-drug interaction, food effect, and PK in specific population are the same as that in Seasonique and LoSeasonique labels.

The major difference between the proposed label and that of the other product is the inclusion of the PK information (i.e., trough concentration of EE) from the Phase I study conducted in this NDA in comparison to Seasonique and LoSeasonique as shown in **Figure 1**.

Figure 1: Model-Predicted Trough Concentrations of Ethinyl Estradiol Following Administration of Quartette, Seasonique, or LoSeasonique



Recommendation:

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, RP.h., Ph.D.

Reviewing Clinical Pharmacologist Date

Myong-Jin Kim, Pharm.D.

Secondary Reviewer Date

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

/s/

SAYED AL HABET
07/26/2012

MYONG JIN KIM
07/27/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204061	**Applicant: Teva Branded Pharmaceutical Products R&D, Inc**	**Stamp Date: May 31, 2012**
Drug Name: Quartette	**NDA/BLA Type: Standard NDA**	**Goal Date: March 31, 2013**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			The general format used by the sponsor for this application is electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The sponsor submitted the label in PLR format in Section 1.14.1
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			The Sponsor has submitted an ISS as requested.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	This supplement includes a single pivotal study; therefore, ISE summaries are not essential for a substantive review to begin.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				The sponsor indicated that this application is a 505(b)(1). This is

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

<table>
<tr><th></th><th>Content Parameter</th><th>Yes</th><th>No</th><th>NA</th><th>Comment</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>appropriate and acceptable.</td></tr>
<tr><td colspan="6">DOSE</td></tr>
<tr><td>13.</td><td>If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?
Study Number: DR-ASC-201
Study Title: A Prospective, Multicenter, Double-Blinded, Randomized Study to Evaluate Bleeding Patterns in Women Using One of Three Different Ascending EE Dose Extended Cycle (91-Day) Oral Contraceptive Regimens (DR-103) Compared to Seasonale®
Sample Size: N=567 (448 completed at least 1 cycle)
<table>
<tr><th>Group</th><th>Dosing x 2 (Two 91-day cycles)</th></tr>
<tr><td>I</td><td>42 days - LNG/EE 150 mcg/20mcg then
21 days - LNG/EE 150 mcg/25mcg then
21 days - LNG/EE 150 mcg/30mcg then
7 days - EE 10 mcg</td></tr>
<tr><td>II</td><td>21 days - LNG/EE 150 mcg/20mcg then
42 days - LNG/EE 150 mcg/25mcg then
21 days - LNG/EE 150 mcg/30mcg then
7 days - EE 10 mcg</td></tr>
<tr><td>III</td><td>21 days - LNG/EE 150 mcg/20mcg then
21 days - LNG/EE 150 mcg/25mcg then
42 days - LNG/EE 150 mcg/30mcg then
7 days - EE 10 mcg</td></tr>
<tr><td>IV</td><td>84 days - LNG/EE 150 mcg/30mcg then
7 days - placebo</td></tr>
</table>
LNG=Levonorgestrel, EE=Ethinyl Estradiol</td><td>X</td><td></td><td></td><td>The Sponsor submitted this Phase 2 dose ranging study in section 5.3.4.1</td></tr>
<tr><td colspan="6">EFFICACY</td></tr>
<tr><td>14.</td><td>Do there appear to be the requisite number of adequate and well-controlled studies in the application?
Pivotal Study: A multicenter, open-label study to evaluate the efficacy and safety of a combination oral contraceptive regimen (DR-103) for the prevention of pregnancy in women (n=3597)</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>15.</td><td>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?</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>16.</td><td>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>17.</td><td>Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</td><td></td><td></td><td>X</td><td>All sites in the submitted studies were in the USA.</td></tr>
<tr><td colspan="6">SAFETY</td></tr>
<tr><td>18.</td><td>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>19.</td><td>Has the applicant submitted adequate information to assess</td><td></td><td></td><td>X</td><td></td></tr>
</table>

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			The Division requires at least 200 subjects completing 13 cycles and a minimum of 10,000 28-day cycles. The Sponsor submitted data on 2183 subjects who completed 13 cycles. Overall, this provided data on the equivalent of 34,354 (28-day) cycles of exposure.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			The Sponsor used MedDRA coding dictionary. (Version 9.0 for their Phase 2 trial and Version 14.0 for their Phase 3 trial)
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Yes, the Sponsor included CRFs of the subjects who became pregnant.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- You used two different MedDRA versions for the ISS datasets: Version 9.0 for Trial DR-ASC-201 and Version 14.0 for Trial DR-103-301. This prevents performance of an integrated safety analysis of these two trials. Submit the ISS datasets using unified MedDRA coding (all adverse events coded in MedDRA Version 14).
- You reported only two categories of protocol deviations: “Received a prohibited medication” and “Overall compliance.” Provide complete information on other protocol deviations, or explain why the data are not available.
- Clarify the meaning of the term ‘combination IP’ as applied to calculations of ‘On-drug’ pregnancy. The Division requests that the Pearl Index include all pregnancies conceived within 7 days after intake of the LAST TABLET – whether it is a combined EE/LNG tablet or EE alone (or placebo). On-drug pregnancies are those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than seven days after the last tablet taken (whether the combination or EE-alone tablet).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

An incomplete cycle in which a subject become pregnant should be considered a complete cycle for all pregnancy calculations. Evaluable cycles should exclude any 28-day cycles in which back-up contraception was used.

Vaishali Popat MD, MPH	July 25, 2012
Reviewing Medical Officer	Date
Lisa Soule, MD	July 25, 2012
Clinical Team Leader	Date

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

/s/

VAISHALI B POPAT
07/25/2012

LISA M SOULE
07/25/2012