Final
(February 22, 2013)
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 204061	**Date of Submission:** May 31, 2012 (cover letter)
Generic Name:	Levonorgestrel (LNG)/ ethinyl estradiol (EE)
Proposed Brand Name:	Quartette™
Formulation:	Tablet
Strengths:	150 mcg/20 mcg, 150 mcg/25 mcg, and 0.15 mg/3 mcg LNG/EE, and 10 mcg EE
OCP Division:	Division of Clinical Pharmacology 3
Office of New Drugs (OND):	Division of Reproductive and Urologic Products
Route of Administration:	Oral
Indication:	Prevention of Pregnancy
Dosage and Administration:	QD for 91 days
Type of Submission:	**Original** NDA, 505b(2)
Sponsor:	Teva Pharmaceuticals Frazer, PA
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Secondary Reviewer:	Myong-Jin Kim, Pharm.D.
Pharmacometrics Reviewer:	Jeff Florian, Ph.D.
Pharmacometrics Secondary Reviewer:	Yaning Wang, Ph.D.

Reference ID: 3265296

TABLE OF CONTENTS

Reference ID: 3265296

1. Executive Summary

This is an original NDA for 91 days extended-regimen and new strengths of the approved formulations and combination oral contraceptives -COCs (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 only, and a second set contains EE alone for 7 days regimen only (total regimen is 91 days). The tablets will be identified by four different colors as follows:

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

The sponsor's rationale for this extended-regimen is that the gradual increase in EE may decrease breakthrough bleeding and spotting.

From the clinical pharmacology perspective, the sponsor crossed referenced three products: Seasonale®, Seasonique®, and LoSeasonique®. These products were manufactured by the same technology and at the same manufacturing site as the proposed product. Therefore, from the pharmacokinetics (PK) perspective, the sponsor conducted one PK study to investigate the relative bioavailability of the three tablet strengths following a single dose (Study DR-103-101, also known as (b) (4) study 10936010).

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable.

1.2 Phase 4 Commitments/Requirements

From the Clinical Pharmacology perspective, no post-marketing commitments/requirements are indicated for this NDA.

1.3 Summary of Important Clinical Pharmacology Findings

A single increasing dose, three-period, relative bioavailability study for the three tablet strengths was conducted in 18 healthy women after overnight fast. At each treatment period, women received two tablets of the respective strengths (i.e., twice the proposed daily dose) as follows:

Treatment A (2 x LNG 150 mcg/EE 20 mcg tablets)
Treatment B (2 x LNG 150 mcg/EE 25 mgg tablets)
Treatment C (2 x LNG 150 mcg/EE 30 mcg tablets).

Reference ID: 3265296

The LNG profiles following the three treatments were superimposed indicating equivalency in the systemic delivery from the three strengths. The 90% CI for the three treatments were within 80% to 125%.

For EE, there was a proportional increase in the systemic EE with increasing dose for the 20, 25, and 30 mcg tablets. The mean C_{max} of EE was 85.8, 105.7, and 123.0 pg/mL after treatment A, B, and C, respectively. The mean AUC (0-inf) was 939.2, 1166.1, and 1409.6 pg.h/mL after treatment A, B, and C, respectively.

Study DR-ASC-201 evaluated the effects of all three ascending EE dose regimens with 150 mcg LNG and Seasonale® (150 mcg LNG and 30 mcg EE) on bleeding/spotting in 567 subjects. There was no statistical difference in reducing bleeding and spotting events between the treatments with Quartette and the marketed extended-cycle product, Seasonale® following two consecutive 91-day cycle treatments (Phase II Study DR-ASC-201).

Based on Phase III study, the overall Pearl Index was 3.19. Further analysis reveals that higher body weight (>90 kg) and race (African American females) may be associated with a higher Pearl Index, although the number of subjects in these subgroups hinder interpretation of this observation from the Phase III study.

2.0 Question-Based Review (QBR)

Overview:

What Is Submitted in this NDA?

As stated earlier, the sponsor cross referenced three previously approved extended-cycle products containing LNG and EE. These products are marketed by the current sponsor (Teva). In addition, the proposed product will be formulated using the same technology and manufacturing site as that of marketed product, Seasonique®. The formulations of Seasonique® and the proposed product are identical, except with the varying amount of EE and the lactose (see biopharmacetics **Section 2.1** for details). The three marketed products and the proposed to-be-marketed tablets are different in terms of EE and LNG contents and the regimen as shown in **Table 2.1**.

Table 2.1 Comparison of Dosage Regimen of Cross Referenced Products

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 84: 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

What is the Sponsor's Rationale for the proposed Regimen?

The sponsor's rationale for the proposed regimen is that the gradual increase in EE dose may provide improved control against breakthrough bleeding or spotting than sustained lower concentrations of EE as would be expected from a product such as LoSeasonique (20 mcg). Furthermore, the stepwise increase may provide improvement in breakthrough bleeding or spotting compared to the persistently higher concentrations of EE in Seasonique (30 mcg), which may also desensitize the estrogen receptors.

In support of this application, the sponsor submitted one PK study (DR-103-101) to evaluate the relative bioavailability of LNG and EE components of each of the three tablet strengths. In addition the sponsor conducted one Phase 2 study to investigate the bleeding patterns of three ascending dose regimens (Study # DR-ASC-201) and one Phase III safety and efficacy study (DR-ASC-301).

What is the Relative Bioavailability of the Three Dosage Strengths?

Study DR-103-101 was conducted to evaluate the relative bioavailability of LNG and EE components of each of the three tablet strengths. This was a single dose study conducted in 18 healthy, non-pregnant females. Subjects were fasted overnight prior to dosing in each of the three treatment periods. There was a 28-day washout period following each period. All subjects received the following treatments:

Period 1 (Test A): 2 x LNG/EE 0.15 mg/**0.020** mg tablets (**Treatment A**)
Period 2 (Test B): 2 x LNG/EE 0.15 mg/**0.025** mg tablets (**Treatment B**)
Period 3 (Test C): 2 x LNG/EE 0.15 mg/**0.030** mg tablets (**Treatment C**)

Out of 18 subjects, 16 subjects completed all 3 periods of the study (see **Appendix 4.2** for details).

The mean concentration-time profiles and PK parameters of LNG and EE are shown in **Figures 2.1-2.6** and **Tables 2.2-9**. From these data the following observations can be made:

Reference ID: 3265296

LNG Data:

- The three tablet strengths contain the same amount of LNG (i.e., 150 mcg). The plasma concentration-time profiles are similar over 0-24 hours (**Figure 2.1**) and over 96 hours (**Figure 2.2**). The mean PK parameters are similar following the three treatments (**Table 2.2**). Also, the 90% CI for all comparisons (A vs B, A vs C, and B vs C) are within 80% to 125% (**Tables 2.3-2.5**).

Figure 2.1 Mean Plasma Concentration-Time Profiles of LNG Over 0-24 h (Study DR-103-101, n=17)

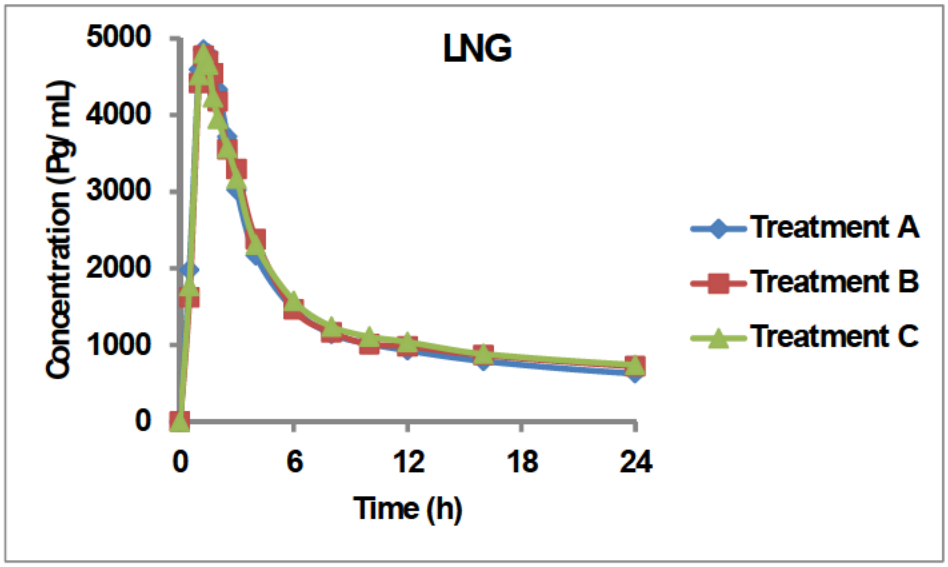
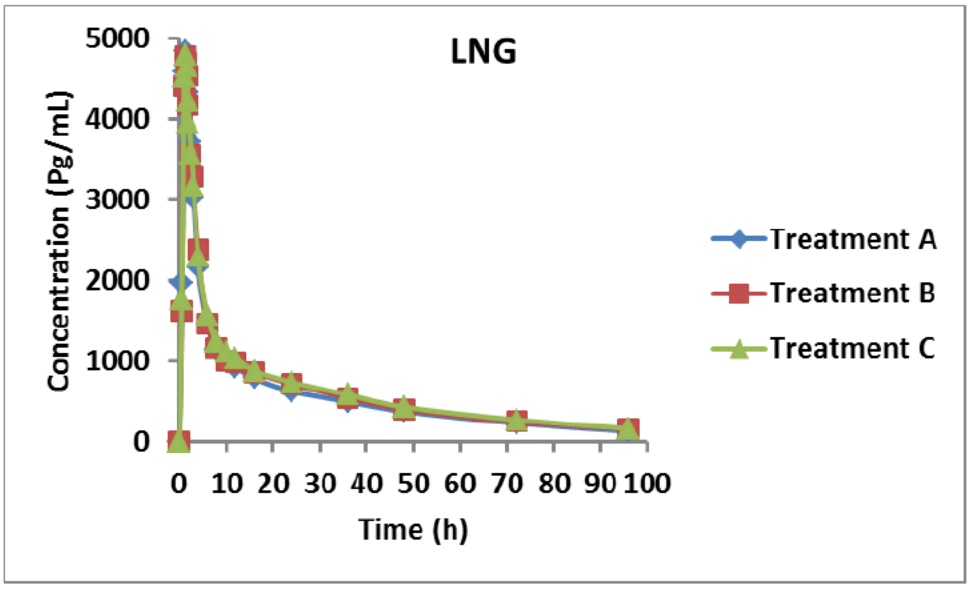


Figure 2.2. Mean Plasma Concentration-Time Profiles of LNG Over 0-96 h (Study DR-103-101, n=17)



Reference ID: 3265296

Table 2.2 Summary of PK Parameters of LNG (n= 17, Study DR-103-101)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)		
	Test A	Test B	Test C*
AUC0-t (pg.hr/mL)	55690.7814 ± 26635.6777 (47.8278)	59850.6338 ± 28702.4085 (47.9567)	62295.7370 ± 28544.0688 (45.8203)
AUC0-inf (pg.hr/mL)	65225.9793 ± 30769.3406 (47.1734)	69175.2308 ± 31614.6258 (45.7022)	72040.1825 ± 29899.8917 (41.5045)
Cmax (pg/mL)	5154.1176 ± 1438.9408 (27.9183)	5250.0000 ± 1855.9398 (35.3512)	5231.2500 ± 1647.2315 (31.4883)
Tmax (hr)	1.3824 ± 0.3762 (27.2162)	1.5294 ± 0.5512 (36.0369)	1.4063 ± 0.4905 (34.8825)
Kel (1/hr)	0.0212 ± 0.0075 (35.2218)	0.0205 ± 0.0080 (38.7536)	0.0200 ± 0.0079 (39.4130)
Elimhalf (hr)	36.4110 ± 12.0135 (32.9942)	37.9438 ± 12.3927 (32.6606)	41.0823 ± 20.8358 (50.7174)

*N=16 for all pharmacokinetic parameters for Test C.

Table 2.3 Treatment A and B Geometric Means, Ratio of Means, and 90% CI for LNG (Study DR-103-102 n = 17)

Parameter	Test B	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	54161.29	50358.93	1.0755	1.0036 - 1.1526	9.1560
AUC0-inf (pg.hr/mL)	63162.53	59010.16	1.0704	1.0034 - 1.1418	7.5681
Cmax (pg/mL)	4956.49	4965.43	0.9982	0.9175 - 1.0860	11.8463

Table 2.4 Treatment A and C Geometric Means, Ratio of Means, and 90% CI for LNG (Study DR-103-102, n= 17)

Parameter	Test C*	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	57845.29	50358.93	1.1487	1.0702 - 1.2329	14.8746
AUC0-inf (pg.hr/mL)	69137.20	59010.16	1.1716	1.0967 - 1.2517	13.3343
Cmax (pg/mL)	5019.73	4965.43	1.0109	0.9274 - 1.1020	17.4101

*N=16 for all pharmacokinetic parameters for Test C.

Reference ID: 3265296

Table 2.5 Treatment B and C Geometric Means, Ratio of Means, and 90% CI for LNG (Study DR-103-102, n=17)

Parameter	Test B	Test C*	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	54161.29	57845.29	0.9363	0.8723 - 1.0050	11.4290
AUC0-inf (pg.hr/mL)	63162.53	69137.20	0.9136	0.8551 - 0.9760	12.0817
Cmax (pg/mL)	4956.49	5019.73	0.9874	0.9058 - 1.0763	14.3463

*N=16 for all pharmacokinetic parameters for Test C.

EE Data:

- The study demonstrated proportional increases in EE concentration that were dose-dependent relative to the tablet EE content over 0-24 h (**Figure 2.3)** and over 0-96 h **(Figure 2.4**). The bar graphs also show the relationship between EE content (dose) of each tablet and C_{max} (**Figure 2.5**) and AUC 0-inf (**Figure 2.6**).

Figure 2.3. Mean Plasma Concentration-Time Profiles of EE Over 0-24 h (Study DR-103-101, n=17)

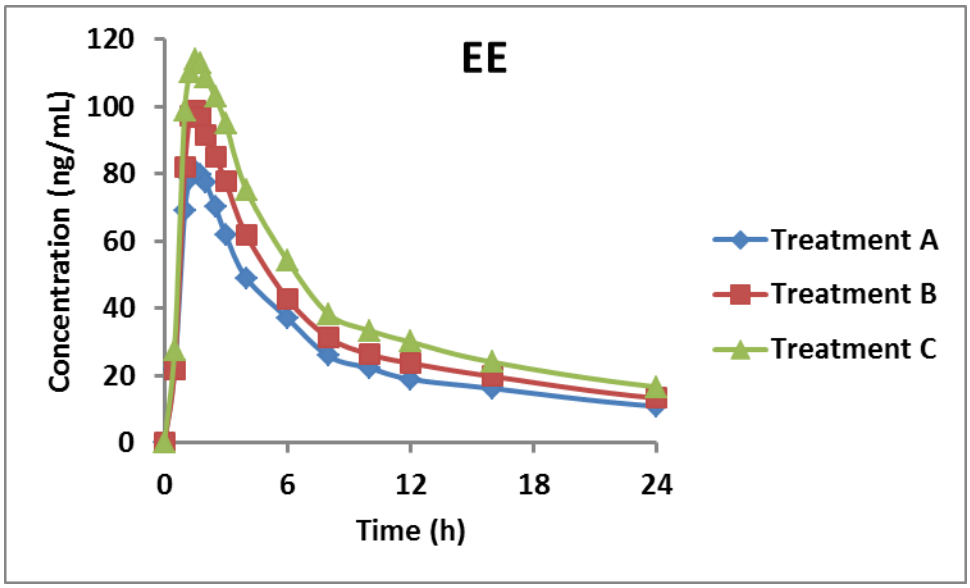


Figure 2.4. Mean Plasma Concentration-Time Profiles of EE Over 0-96 h (Study DR-103-101, n=17)

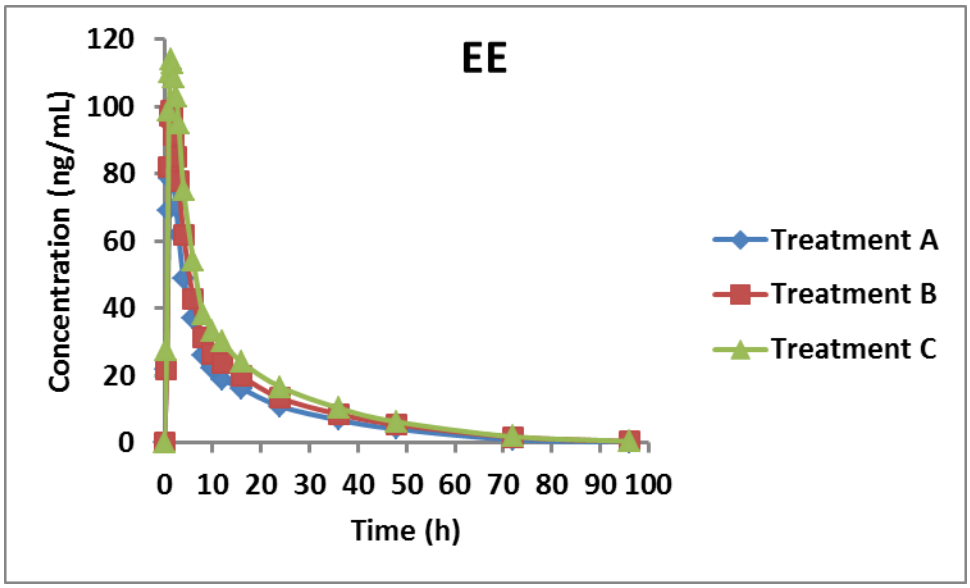


Figure 2.5. Mean EE Cmax (Study DR-103-101, n=17)

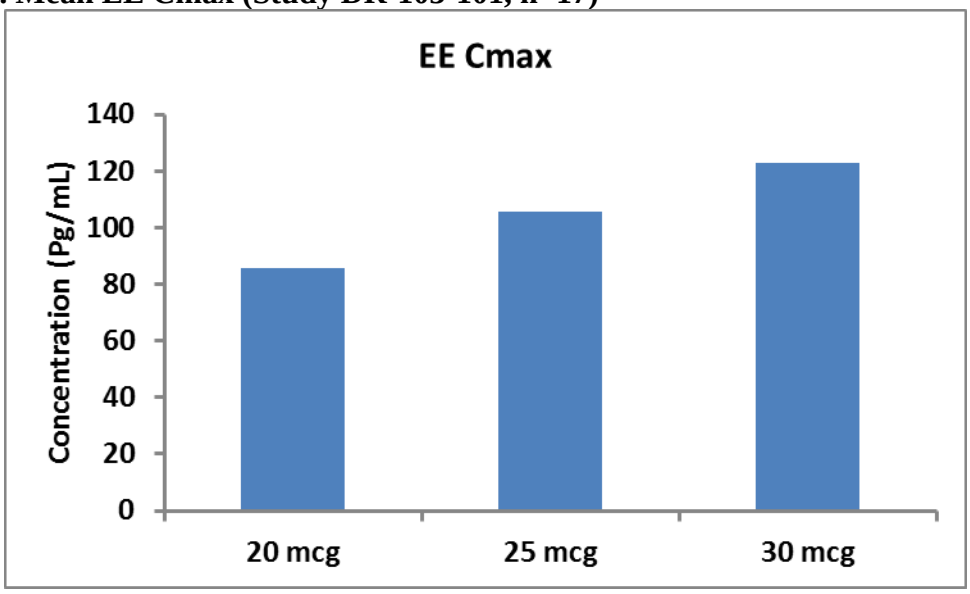


Figure 2.6. Mean EE AUC (0-inf) (Study DR-103-101, n=17)

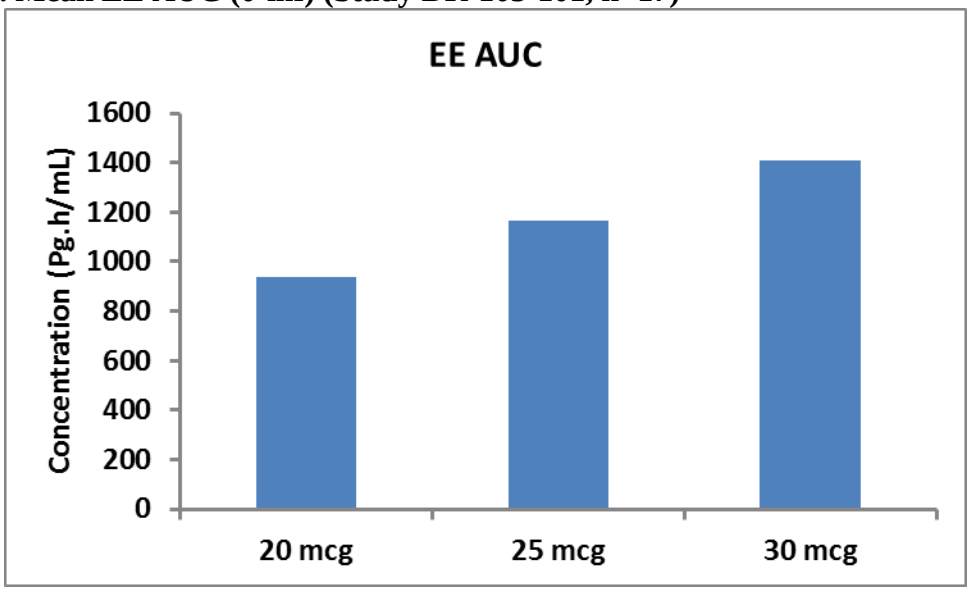


Figure 1.3.3 Dose Normalized Mean Plasma Concentration-Time Profiles of EE (Study DR-103-101, n=17)

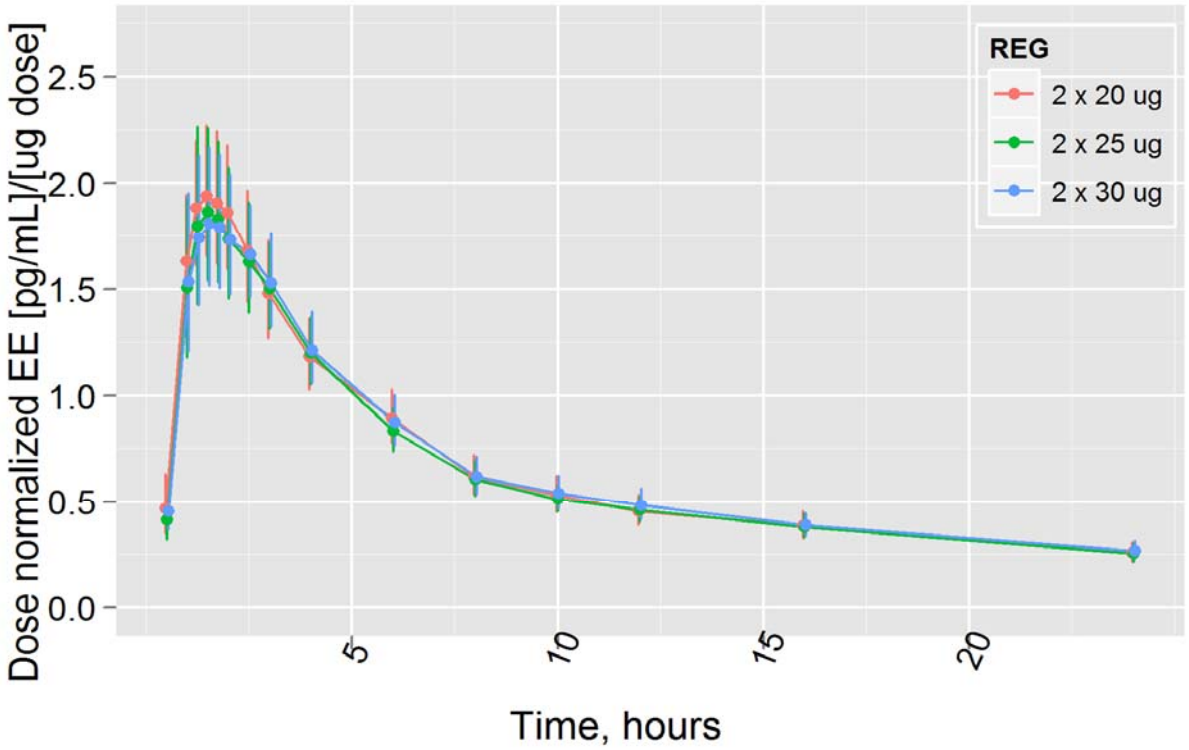


Table 2.6 Summary of PK Parameters of EE (n= 17, Study DR-103-101)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)		
	Test A	Test B	Test C*
AUC0-t (pg.hr/mL)	864.0218 ± 317.4670 (36.7429)	1085.3753 ± 377.5990 (34.7897)	1312.1113 ± 408.6293 (31.1429)
AUC0-inf (pg.hr/mL)	939.1852 ± 327.0875 (34.8267)	1166.0825 ± 393.2429 (33.7234)	1409.6321 ± 434.4092 (30.8172)
Cmax (pg/mL)	85.8471 ± 25.0501 (29.1799)	105.7353 ± 28.6858 (27.1298)	122.9688 ± 30.7610 (25.0153)
Tmax (hr)	1.5882 ± 0.3638 (22.9061)	1.6912 ± 0.4803 (28.4010)	1.6250 ± 0.4378 (26.9414)
Kel (1/hr)	0.0437 ± 0.0096 (21.9147)	0.0410 ± 0.0112 (27.2713)	0.0428 ± 0.0115 (26.9669)
Elimhalf (hr)	16.7150 ± 4.4107 (26.3875)	18.0962 ± 4.8164 (26.6157)	17.3577 ± 4.9386 (28.4520)

*N=16 for all pharmacokinetic parameters for Test C.

- The ratios and 90% CI for the comparison (A vs B, A vs C, and B vs C) are shown in **Tables 2.7-2.9**. These data confirm the continual increase in EE concentrations as expected based on tablets contents of EE.

Table 2.7 Treatment A and B Geometric Means, Ratio of Means, and 90% CI for EE (n=17, Study DR-103-102)

Parameter	Test B	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1031.17	815.56	1.2644	1.2001 - 1.3321	8.0419
AUC0-inf (pg.hr/mL)	1110.77	891.91	1.2454	1.1899 - 1.3035	6.9479
Cmax (pg/mL)	102.11	82.24	1.2415	1.1639 - 1.3244	10.2866

Reference ID: 3265296

Table 2.8 Treatment A and C Geometric Means, Ratio of Means, and 90% CI for EE (n=17, Study DR-103-102)

Parameter	Test C*	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1229.77	815.56	1.5079	1.4312 - 1.5887	9.8496
AUC0-inf (pg.hr/mL)	1325.93	891.91	1.4866	1.4204 - 1.5560	9.1979
Cmax (pg/mL)	114.76	82.24	1.3954	1.3081 - 1.4885	11.0593

*N=16 for all pharmacokinetic parameters for Test C.

Table 2.9. Treatment B and C Geometric Means, Ratio of Means, and 90% CI for EE (n=17, Study DR-103-102)

Parameter	Test B	Test C*	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1031.17	1229.77	0.8385	0.7959 - 0.8834	8.0961
AUC0-inf (pg.hr/mL)	1110.77	1325.93	0.8377	0.8004 - 0.8768	6.5675
Cmax (pg/mL)	102.11	114.76	0.8898	0.8341 - 0.9492	10.9598

*N=16 for all pharmacokinetic parameters for Test C.

As demonstrated above, the plasma concentration-time profiles of LNG was superimposed indicating a consistent release of LNG from the three tablets, each containing 150 mcg LNG. This indicates that all three tablets provide equivalent LNG exposure as the 90% CI falls within the established bioequivalence criteria of 80% to 125%.

In terms of EE, the plasma level increased proportionally as the tablet strength increased from 20 mcg to 30 mcg. When the plasma concentration-time profiles were normalized by dose, a superimposition was demonstrated for all three strengths (**Figure 1.3.3**). In addition, after dose-normalization, the 90% CI for both the C_{max} and AUC falls within the established bioequivalence criteria of 80% to 125% (**Tables 2.10-2.12**).

Table 2.10. Treatments A and B Dose-normalized PK parameters and 90% CI for EE (n=17, Study DR-103-102)

Parameter	Test B (2 x 25 ug)	Test A (2 x 20 ug)	Norm. Ratio	Norm. 90% CI
AUC0-t (pg.hr/mL)	1031.17	815.56	1.012	(0.96 - 1.066)
AUC0-inf (pg.hr/mL)	1110.77	891.91	0.996	(0.952 - 1.043)
Cmax (pg/mL)	102.11	82.24	0.993	(0.931 - 1.06)

Reference ID: 3265296

Table 2.11. Treatments A and C Dose-normalized PK parameters and 90% CI for EE (n=17, Study DR-103-102)

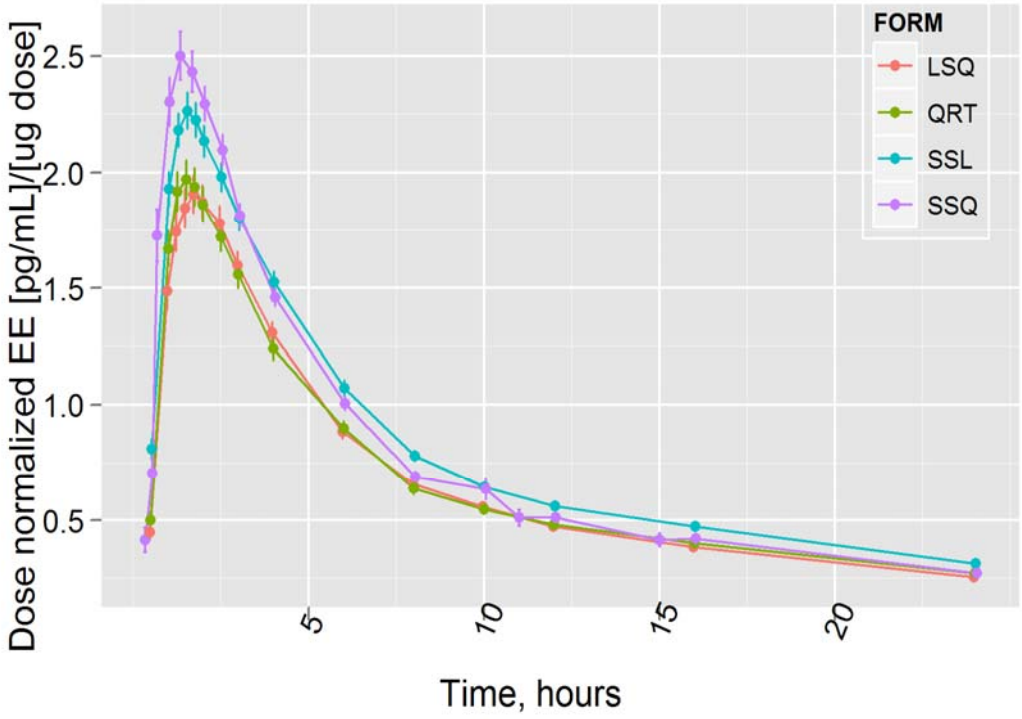
Parameter	Test C (2 x 30 ug)	Test A (2 x 20 ug)	Norm. Ratio	Norm. 90% CI
AUC0-t (pg.hr/mL)	1229.77	815.56	1.005	(0.954 - 1.059)
AUC0-inf (pg.hr/mL)	1325.93	891.91	0.991	(0.947 - 1.037)
Cmax (pg/mL)	114.76	82.24	0.930	(0.872 - 0.992)

Table 2.10. Treatments B and B Dose-normalized PK parameters and 90% CI for EE (n=17, Study DR-103-102)

Parameter	Test B (2 x 25 ug)	Test C (2 x 30 ug)	Norm. Ratio	Norm. 90% CI
AUC0-t (pg.hr/mL)	1031.17	1229.77	1.006	(0.955 - 1.06)
AUC0-inf (pg.hr/mL)	1110.77	1325.93	1.005	(0.96 - 1.052)
Cmax (pg/mL)	102.11	114.76	1.068	(1.001 - 1.139)

Across product analysis reveals that single dose EE exposure from Quartette™ is comparable or slightly lower than LoSeaonique®, which contains 100 mcg LNG and 20 mcg EE (**Figure 1.3.4**). Furthermore, the analysis shows that single dose EE exposure from Seasonique® and Seasonale®, both of which contain 150 mcg of LNG and 30 mcg of EE, is higher than the EE from Quartette™. These differences in exposure are predicted to be present at steady state. In other words, the predicted steady state exposure of EE from Quartette lies between that of already approved products: LoSeasonique® and Seasonique®/Seasonale®.

Figure 1.3.4. Across Product Comparisons of EE Exposure (Dose-Normalized Mean Plasma Concentration-Time Profiles of EE)



Summary of Phase II Bleeding Study (Study DR-103-201):

Does the Data Support the Rationale for the Proposed Dosage Regimen?
Does the Proposed-Dosage Regimen Decrease the Bleeding and Spotting?

As stated earlier, the sponsor conducted Phase II study to evaluate the bleeding patterns in women using one of the proposed regimens compared to the marketed Seasonale® (Study # DR-ASC-201). This study was double-blind, multicenter, four treatments regimen in 567 women.

In the run-in phase of the study, eligible subjects received a 28-day run-in cycle of Portia® (21 days of 30 mcg EE/150 mcg LNG followed by 7 days of placebo). Upon completion of the run-in cycle, subjects were randomly assigned to one of the following four 91-day extended cycle regimens:

Group I (**Low dose**): **42 days** combination active tablets (20 mcg EE /150 mcg LNG) followed by **21 days** combination active tablets (25 mcg EE/150 mcg LNG) followed by **21 days** combination active tablets (30 mcg EE/150 mcg LNG) followed by 7 days of 10 mcg EE tablets, for **two** consecutive 91-day cycles.

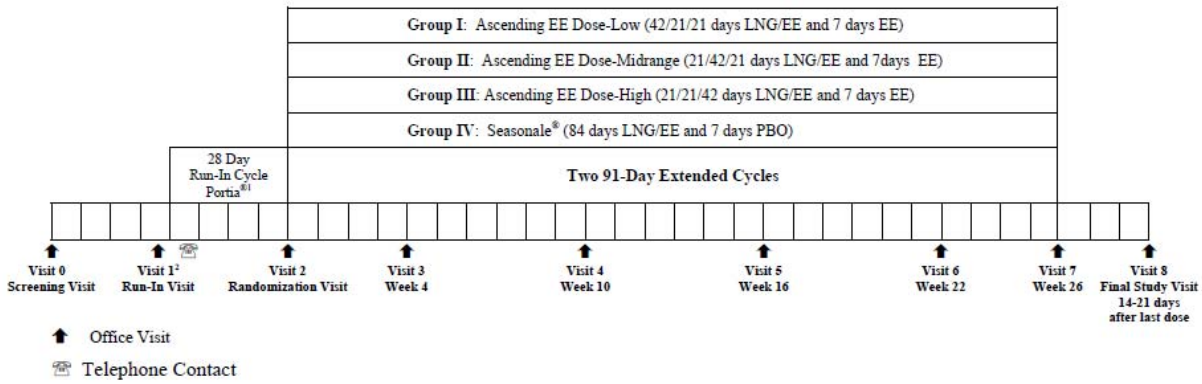
Group II (**Midrange dose**): **21 days** combination active tablets (20 mcg EE /150 mcg LNG) followed by **42 days** combination active tablets (25 mcg EE/ 150 mcg LNG) followed by 21 days combination active tablets (30 mcg EE/150 mcg LNG) followed by 7 days of 10 mcg EE tablets, for **two** consecutive 91-day cycles.

Group III (**High dose**): **21 days** combination active tablets (20 mcg EE /150 mcg LNG) followed by **21 days** combination active tablets (25 mcg EE/150 mcg LNG) followed by 42 days combination active tablets (30 mcg EE/150 mcg LNG) followed by 7 days of 10 mcg EE tablets, for **two** consecutive 91-day cycles.

Group IV (**Seasonale®**): **84 days** of combination active tablets, each containing 30 mcg EE and 150 mcg LNG, followed by 7 days of placebo tablets, for two consecutive 91-day cycles.

The schematic below represents the overall study design:

Scheme: Overall study design (Study # DR-ASC-201)



[1] To start on the Sunday following the start of menses after the Run-In Visit
[2] ≤ 28 days from visit 0

End-Points Measurements:

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.

Overall, there was a slight improvement in bleeding and/or spotting patterns in the three ascending proposed EE regimen compared to Seasonale® (**Figure 2.7**, see Medical Officer's review for details). However, there was no statistical improvement in these events between the treatment arms.

Reference ID: 3265296

Figure 2.7 Proportion of Subjects with Bleeding and/or Spotting (B/S) by Each Day During 84-Day Active Cycle (Phase II Study, DR-ASC-201, source study report Page 60).

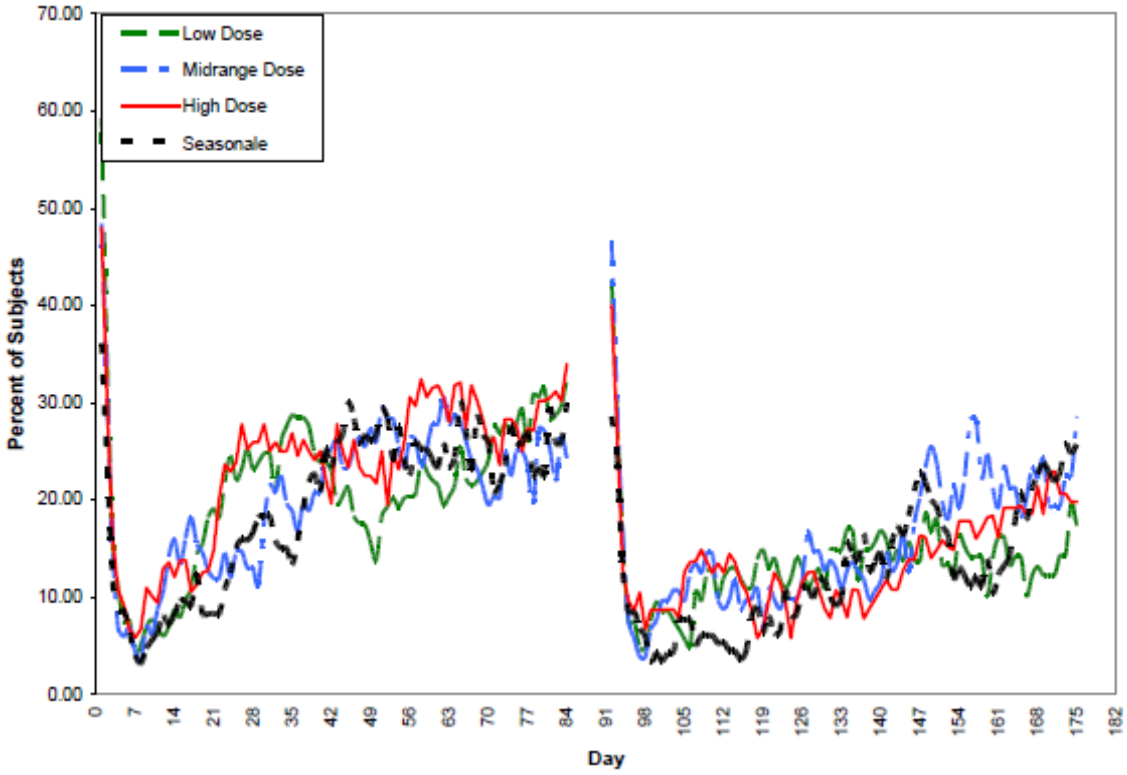


Table 2.10. Average of Bleeding and/or Spotting (B/S) Severity by Each Active Cycle and Run-in-Period (Phase II Study, DR-ASC-201, source study report Page 61).

Cycle/Status	Low dose	Midrange 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%

Note: Bleeding/Spotting Score 0-4: None to Heavy

Percentage change = (Average B/S severity at Run-in – Average B/S severity at each active cycle) / Average B/S severity at Run-In.

The results of this study showed a small and but not statistically significant difference with the proposed product compared to the marketed product, Seasonale® in terms of bleeding and/or spotting. The data do not appear too convincing based on the original rationale for the development of this extended-cycle product that implies improvement of bleeding and/or spotting over the existing marketed products.

Summary of Phase III Study (Study # DR-103-301):

Phase III study was conducted in 3597 women for 12 months. The Pearl Index from this study is shown below in **Table 2.11**.

Table 2.11. Pear Index in Phase III study as reported by the sponsor and Internally (Study DR-103-301)

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
Applicant	2992	67	30363	1848	28515	3.05	(2.37, 3.88)
Reviewer (MO)	2992	70	30363	1848	28515	3.19	(2.49, 4.03)

The clinical significance of the bleeding and/or spotting data from Phase II study is questionable at this time (see the Medical Officer's final review for details). Also, further discussion of the Pearl Index and the impact of various subgroups on response are discussed later in this review and in more detail in **Appendix 4.3.1**.

What is the Magnitude of the Pearl Index in Comparison to Marketed Products?

The primary PK study 101 demonstrated dose proportionality of EE and equivalency of LNG in the three dosage strengths. As we discussed earlier, Phase II data related to bleeding patterns and spotting were not statistically significant comparing to Seasonale®. The Pearl Index for the four products (three previously approved) is listed below.

Product	Pearl Index
Quartette™ (150 mcg LNG/20, 25, and 30 mcg EE)	3.19 (FDA analysis)
Seasonale® (150 mcg LNG/30 mcg EE)	1.98
Seasonique® (150 mcg LNG/30 mcg EE)	1.77
LoSeasonique® (100 mcg LNG/20 mcg EE)	4.58

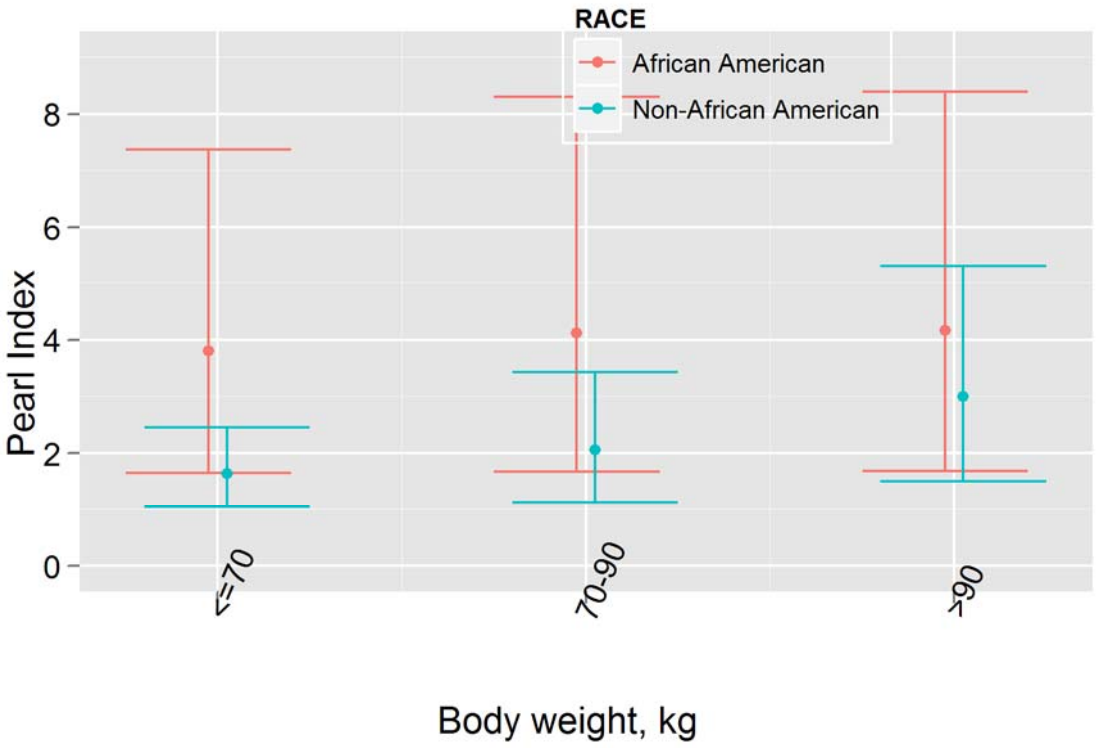
As shown in the above table, the Pearl Index for the proposed product is higher than Sesoanale® and Seasonique®, both of which contain 150 mcg LNG and 30 mcg of EE. However, it is lower than the Pearl Index from LoSeasonique®, which contains 100 mcg of LNG and 20 mcg of EE. Considering the variability in the study designs among the four products, the Pearl Index of the proposed product falls within the approved products.

Summary of Pharmacometric Analysis:

According to the pharmacometric analysis the following conclusions were made which are consistent with the conclusions in this review:

- **Bleeding:** There were no distinct differences in the incidence of bleeding or spotting between the three multiple ascending dose arms evaluating in Phase IIb. The sponsor selected the minimum cumulative dose arm for further evaluation in Phase III.
- **Exposure:** Base on the PK data from study 101, each of the ascending dose arms evaluated in the Phase II study have predicted EE exposures that fall between the EE exposures of two already approved oral contraceptives (Seasonique® and Lo-Seasonique®).
- **Efficacy:** Body weight >90 kg and African American race were associated with an increased Pearl Index. Further analysis of the impact of body weight on Pearl Index was performed based on the sponsor's response that the higher Pearl Index in African Americans was due to higher body weight, and consequently, lower EE exposures. From this analysis, it appears that the increase in Pearl Index for African Americans is not solely explained by body weight (**Figure 2.8**) (see Pharmacometrics review in **Appendix 4.3.1**).

Figure 2.8 Pearl Index relative to Body Weight and Race (Study DR-103-301, see Appendix 4.3.1)



Pediatric Waiver Request:

The sponsor requested (b) (4) waiver for pediatric studies for this product. According to the class labeling for combined oral contraceptives (COC), the safety and efficacy of LNG and EE tablets and EE tablets have been established in women of reproductive age, and expected to be the same for post-pubertal adolescents under the age of 18 as for users 18 years and older. Use of COC before menarche is not indicated.

2.1 Biopharmaceutics

Description and Composition of the Drug Product:

As stated in this review, the proposed product (Quartette™ , DR-103) is an extended-regimen, oral contraceptive consisting of 84 tablets, each containing 0.15 mg of LNG in combination with 0.02 mg (42 tablets), 0.025 mg (21 tablets), or 0.03 mg (21 tablets) of EE followed by 7 tablets containing 0.01 mg of EE alone.

The formulation of the proposed product is based on the formulation of Seasonique®, which is also marketed by Teva Pharmaceuticals. The difference between Seasonique® and the proposed product is with the varying amount of EE and the amount of lactose monohydrate. Otherwise, both formulations are identical.

Furthermore, the proposed product and Seasonique® will be manufactured at the same site, at the same commercial scale, using the same validated process, the same equipment, and the same in-process controls. It should be noted that the sponsor manufactured 2 batches of each tablet's strength of LNG/EE at the commercial scale for use in clinical studies.

The quantity of the nonfunctional color coat remains the same for all strengths of LNG/EE combination tablets. However, the color of each tablet's strength is different. The physical tablet descriptions for LNG and EE Tablets, USP 0.15 mg/0.02 mg, 0.15 mg/0.025 mg, and 0.15 mg/0.03 mg are shown in **Table 2.1.1.**

Table 2.1.1. Description Tablets

	Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.15 mg/0.02 mg	**Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.15 mg/0.025 mg**	**Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.15 mg/0.03 mg**
Color	Light Pink	Pink	Purple
Description	round, film coated biconvex, unscored tablet	round, film coated biconvex, unscored tablet	round, film coated biconvex, unscored tablet
ID	Debossed with "TV" on one side and "076" on the other side	Debossed with "TV" on one side and "075" on the other side	Debossed with "TV" on one side and "074" on the other side
Weight	85 mg	85 mg	85 mg

The quantitative compositions of LNG and EE Tablets are shown in **Tables 2.1.2-4**.

Table 2.1.2. Composition of LNG 0.15/EE 0.02 Tablets

Ingredient	mg/Tablet	w/w (%)
Levonorgestrel, USP (b) (4)	0.15	(b) (4)
Ethinyl Estradiol, USP (b) (4)	0.02	
Anhydrous Lactose, NF (b) (4)	(b) (4	
Hypromellose (b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Magnesium Stearate, NF		
Total Core Weight (mg) (b) (4		
Total Coated Tablet Weight (mg) (b) (4)	85.00	100

Table 2.1.2. Composition of LNG 0.15/EE 0.025 Tablets

Ingredient	mg/Tablet	w/w (%)
Levonorgestrel, USP (b) (4)	0.15	(b) (4)
Ethinyl Estradiol, USP (b) (4)	0.025	
Anhydrous Lactose, NF (b) (4)	(b) (4)	
Hypromellose (b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Magnesium Stearate, NF		
Total Core Weight (mg) (b) (4)		
Total Coated Tablet Weight (mg) (b) (4)	85.00	100

Table 2.1.3. Composition of LNG 0.15/EE 0.03 Tablets

Ingredient	mg/Tablet	w/w (%)
Levonorgestrel, USP (b) (4)	0.15	(b) (4)
Ethinyl Estradiol, USP (b) (4)	0.03	
Anhydrous Lactose, NF (b) (4)	(b) (4)	
Hypromellose (b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Magnesium Stearate, NF		
Total Core Weight (mg) (b) (4)		
Total Coated Tablet Weight (mg) (b) (4)	85.00	100

Study DR-103-101 was conducted specifically to evaluate the relative bioavailability of these three strengths (see **Appendix 4.2** for detail discussion of this study).

2.2 Analytical Methods

LNG and EE plasma samples were analyzed by a validated HPLC with MS/MS detection method at (b) (4). All the accuracy and reproducibility measures are within the acceptable ranges for EE and LNG.

3.0 Detailed Labeling Recommendations

Labeling comments will be made directly into the label during the internal labeling meetings and discussion with the sponsor.

It should be noted that 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.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Individual Study Review (Selected Studies)

4.2.1 Study DR-103-101 (Relative BA)

Title: "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"

Objective:

The objective of this study was to evaluate the relative bioavailability of three different dosage strengths of DR-103 (LNG/EE) tablet formulation under fasted conditions in healthy, non-tobacco using,adult female subjects.

Design:

This was a single increasing dose, three-periods, bioavailability study conducted with 18 (16 completing all 3 periods) healthy, non-tobacco using, adult female subjects. There were 28-day intervals between treatments. All subjects fasted overnight and received the following treatments as follows:

Period 1 (Test A): 2 x LNG/EE 0.15 mg/0.020 mg tablets (**Treatment A**)
Period 2 (Test B): 2 x LNG/EE 0.15 mg/0.025 mg tablets (**Treatment B**)
Period 3 (Test C): 2 x LNG/EE 0.15 mg/0.030 mg tablets (**Treatment C**)

Drug Administration:

Out of 18 subjects, 16 subjects completed all 3 periods of the study. Sixteen (16) subjects completed all 3 periods of the study. Subjects fasted for at least 2 hours before tablet administration. Tablets were administered with 240 mL water at approximately 22:00 hour. Then subjects were served snack at approximately 30 minutes later.

PK Samples:

Blood samples for determination of LNG and EE concentrations were collected at pre-dose and at appropriate intervals over 96 hours after dosing in each period. Blood was collected at each period at the following time points: pre-dose (up to 60 minutes prior to dosing) and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96 hours post dosing.

Subjects:

A total of 18 healthy females were entered into this study and 16 subjects completed all 3 periods. These 18 females were 18-45 years of age inclusive with a Body Mass Index (BMI) 18-30 kg/m2 were included in the study. All females were in their normal menstrual cycle and were

Reference ID: 3265296

either abstained from sexual intercourse or use reliable non-hormonal method of contraception. The demographic characteristic of the subjects is shown in the table below:

SUBJECTS INCLUDED IN THE STATISTICAL ANALYSIS OF LEVONORGESTREL AND ETHINYL ESTRADIOL			
Parameter	**Test A N = 17**	**Test B N = 17**	**Test C N = 16**
Gender			
Males	0 (0.00%)	0 (0.00%)	0 (0.00%)
Females	17 (100.00%)	17 (100.00%)	16 (100.00%)
Ethnicity			
Hispanic/Latino	6 (35.29%)	6 (35.29%)	6 (37.50%)
Not Hispanic/Latino	11 (64.71%)	11 (64.71%)	10 (62.50%)
Race			
American Indian/Alaskan Native	0 (0.00%)	0 (0.00%)	0 (0.00%)
Asian	0 (0.00%)	0 (0.00%)	0 (0.00%)
Black	11 (64.71%)	11 (64.71%)	10 (62.50%)
Native Hawaiian or other Pacific Islander	0 (0.00%)	0 (0.00%)	0 (0.00%)
White	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	6 (35.29%)	6 (35.29%)	6 (37.50%)
Age (years)			
Mean ± SD	26.65 ± 6.55	26.65 ± 6.55	26.00 ± 6.18
Median	25.00	25.00	25.00
Range	19 - 39	19 - 39	19 - 39
Age Groups			
< 18	0 (0.00%)	0 (0.00%)	0 (0.00%)
18 – 40	17 (100.00%)	17 (100.00%)	16 (100.00%)
41 – 64	0 (0.00%)	0 (0.00%)	0 (0.00%)
65 – 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
> 75	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight (lbs)			
Mean ± SD	151.76 ± 24.04	151.76 ± 24.04	150.13 ± 23.82
Median	157.00	157.00	151.50
Range	106 - 195	106 - 195	106 - 195
BMI (Kg/m^2)			
Mean ± SD	25.32 ± 3.98	25.32 ± 3.98	25.06 ± 3.97
Median	26.70	26.70	26.20
Range	18.3 - 29.4	18.3 - 29.4	18.3 - 29.4
Tobacco User[2]			
Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)
No	17 (100.00%)	17 (100.00%)	16 (100.00%)

[1] Determined at screening.
[2] Defined as current tobacco user (having used tobacco within 90 days of first dose).

Reference ID: 3265296

Results:

LNG Data:

The mean concentration-time profiles and PK parameters of LNG and EE are shown in **Figures 4.2.1-4.2.4 and Tables 4.2.1-4.2.10**. From this data the following observations can be made:

LNG Data:

- The three tablet strengths contain the same amount of LNG (i.e., 0.15 mg). The plasma concentration-time profiles are similar over 0-24 hours (**Figure 4.2.1**) and over 96 hours (**Figure 4.2.2**). The mean PK parameters are similar following the three treatments (**Tables 4.2.1-4.2.5**). Also, the 90% CI for all comparisons are within 80% to 125% (**Tables 4.2.3-4.2.5**).

Figure 4.2.1. Mean Plasma Concentration-Time Profiles (0-24h) of LNG

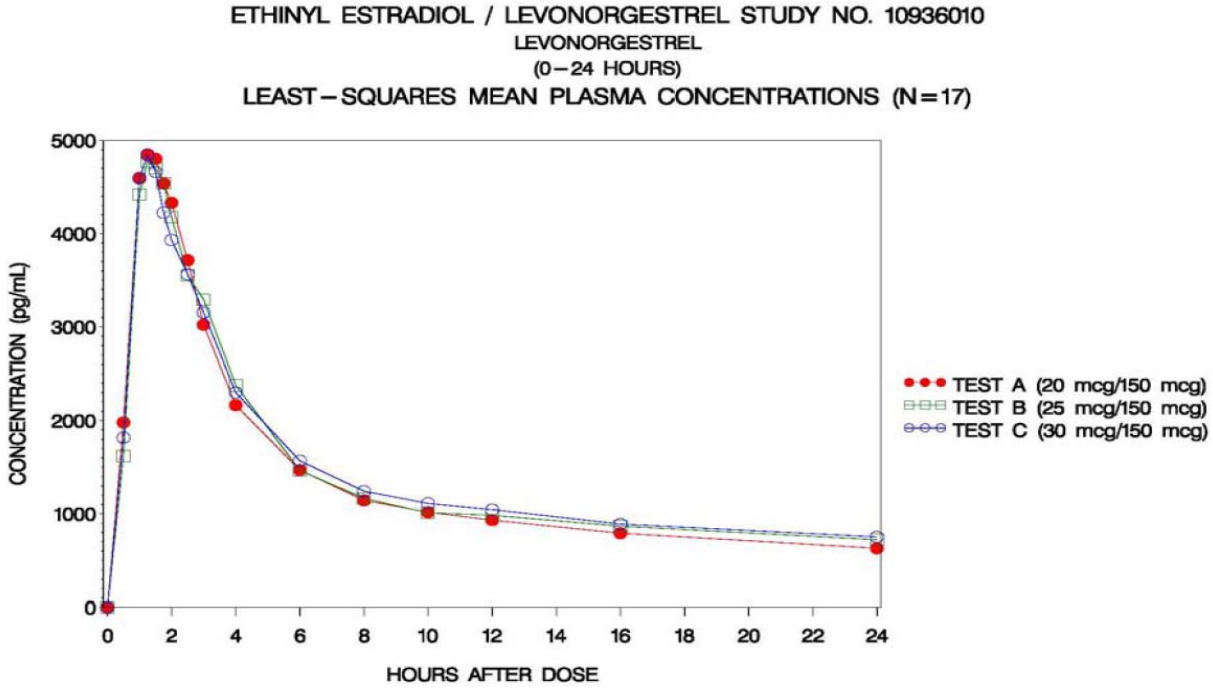


Figure 4.2.2. Mean Plasma Concentration-Time Profiles (0-96h) of LNG

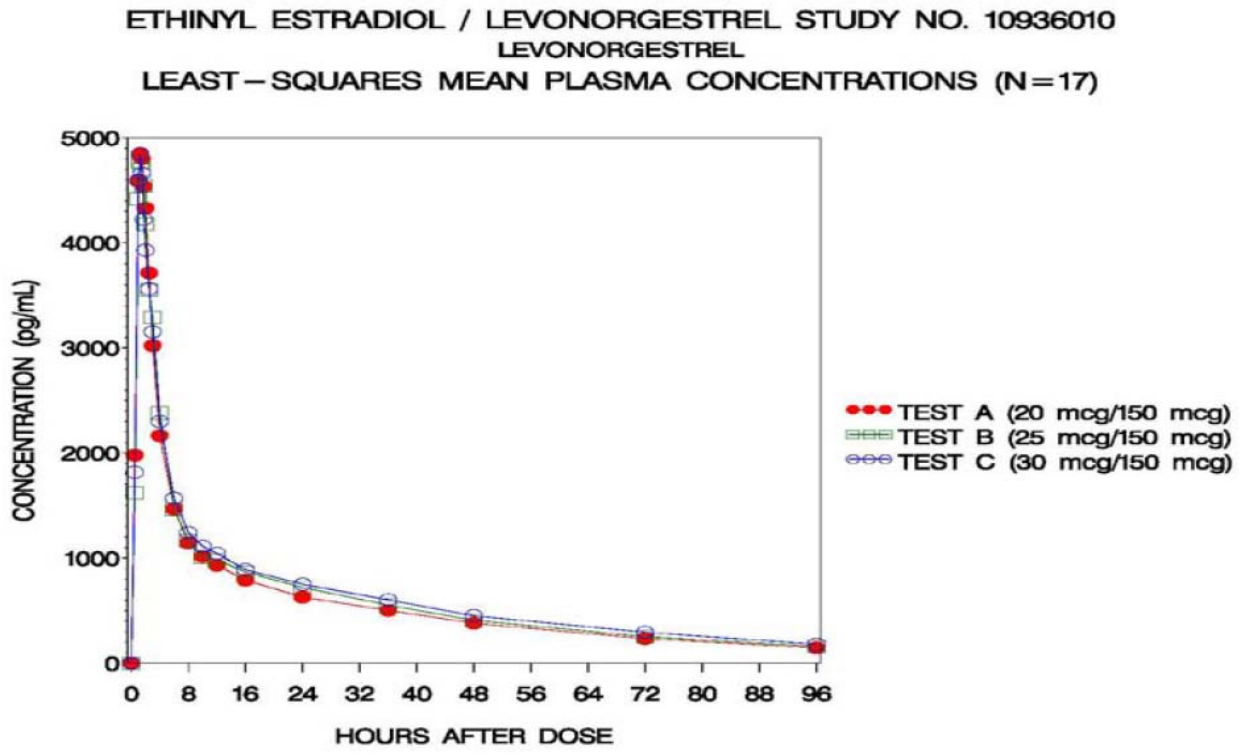


Table 4.2.1. Mean (±SD) PK Parameters of LNG

Summary of Pharmacokinetic Parameters
Untransformed Data
Analyte: Levonorgestrel (N = 17)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)		
	Test A	Test B	Test C*
AUC0-t (pg.hr/mL)	55690.7814 ± 26635.6777 (47.8278)	59850.6338 ± 28702.4085 (47.9567)	62295.7370 ± 28544.0688 (45.8203)
AUC0-inf (pg.hr/mL)	65225.9793 ± 30769.3406 (47.1734)	69175.2308 ± 31614.6258 (45.7022)	72040.1825 ± 29899.8917 (41.5045)
Cmax (pg/mL)	5154.1176 ± 1438.9408 (27.9183)	5250.0000 ± 1855.9398 (35.3512)	5231.2500 ± 1647.2315 (31.4883)
Tmax (hr)	1.3824 ± 0.3762 (27.2162)	1.5294 ± 0.5512 (36.0369)	1.4063 ± 0.4905 (34.8825)
Kel (1/hr)	0.0212 ± 0.0075 (35.2218)	0.0205 ± 0.0080 (38.7536)	0.0200 ± 0.0079 (39.4130)
Elimhalf (hr)	36.4110 ± 12.0135 (32.9942)	37.9438 ± 12.3927 (32.6606)	41.0823 ± 20.8358 (50.7174)

*N=16 for all pharmacokinetic parameters for Test C.

Reference ID: 3265296

Table 4.2.2. Statistical Data of LNG

Statistical Comparisons
Analyte: Levonorgestrel (N = 17)

	Test A	Test B	Test C**
Median Tmax (hour)	1.25	1.25	1.25
AUC0-t/AUC0-inf ratio*	0.8538	0.8652	0.8538
*Ratio calculated as AUC0-t LSmean divided by AUC0-inf LSmean.			

**N=16 for all pharmacokinetic parameters for Test C.

Table 4.2.3. Statistical Data of LNG

Test B versus Test A

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Levonorgestrel (N = 17)

Parameter	Test B	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	54161.29	50358.93	1.0755	1.0036 - 1.1526	9.1560
AUC0-inf (pg.hr/mL)	63162.53	59010.16	1.0704	1.0034 - 1.1418	7.5681
Cmax (pg/mL)	4956.49	4965.43	0.9982	0.9175 - 1.0860	11.8463

Table 4.2.4. Statistical Data of LNG

Test C versus Test A

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Levonorgestrel (N = 17)

Parameter	Test C*	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	57845.29	50358.93	1.1487	1.0702 - 1.2329	14.8746
AUC0-inf (pg.hr/mL)	69137.20	59010.16	1.1716	1.0967 - 1.2517	13.3343
Cmax (pg/mL)	5019.73	4965.43	1.0109	0.9274 - 1.1020	17.4101

*N=16 for all pharmacokinetic parameters for Test C.

Reference ID: 3265296

Table 4.2.5. Statistical Data of LNG

Test B versus Test C

Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data
Analyte: Levonorgestrel (N = 17)

Parameter	Test B	Test C*	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	54161.29	57845.29	0.9363	0.8723 - 1.0050	11.4290
AUC0-inf (pg.hr/mL)	63162.53	69137.20	0.9136	0.8551 - 0.9760	12.0817
Cmax (pg/mL)	4956.49	5019.73	0.9874	0.9058 - 1.0763	14.3463

*N=16 for all pharmacokinetic parameters for Test C.

EE Data:

- The plasma concentration-time profiles of EE increased as expected representing the increase in EE amount of 20, 25, and 30 mcg in each tablet (**Figure 4.2.3-4.2.4 and Tables 4.2.6-4.2.10**).

Figure 4.2.3. Mean Plasma Concentration-Time Profiles (0-24h) of EE

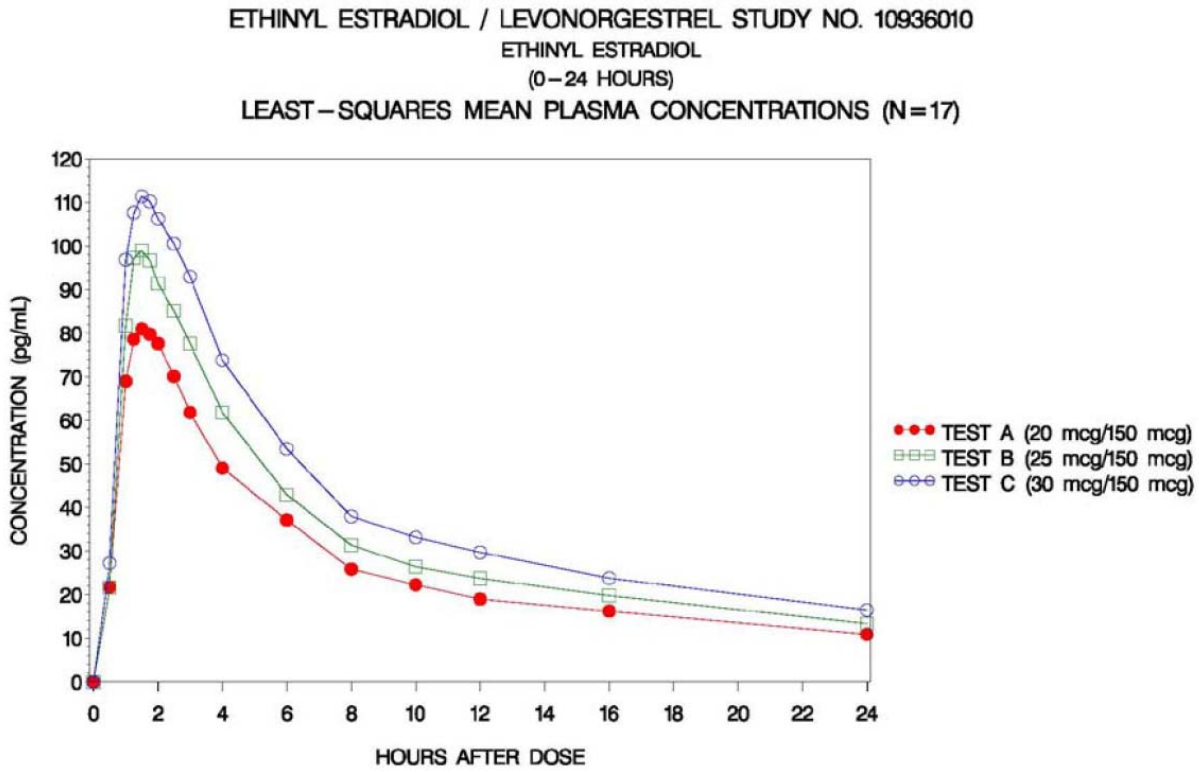


Figure 4.2.4. Mean Plasma Concentration-Time Profiles (0-96h) of EE

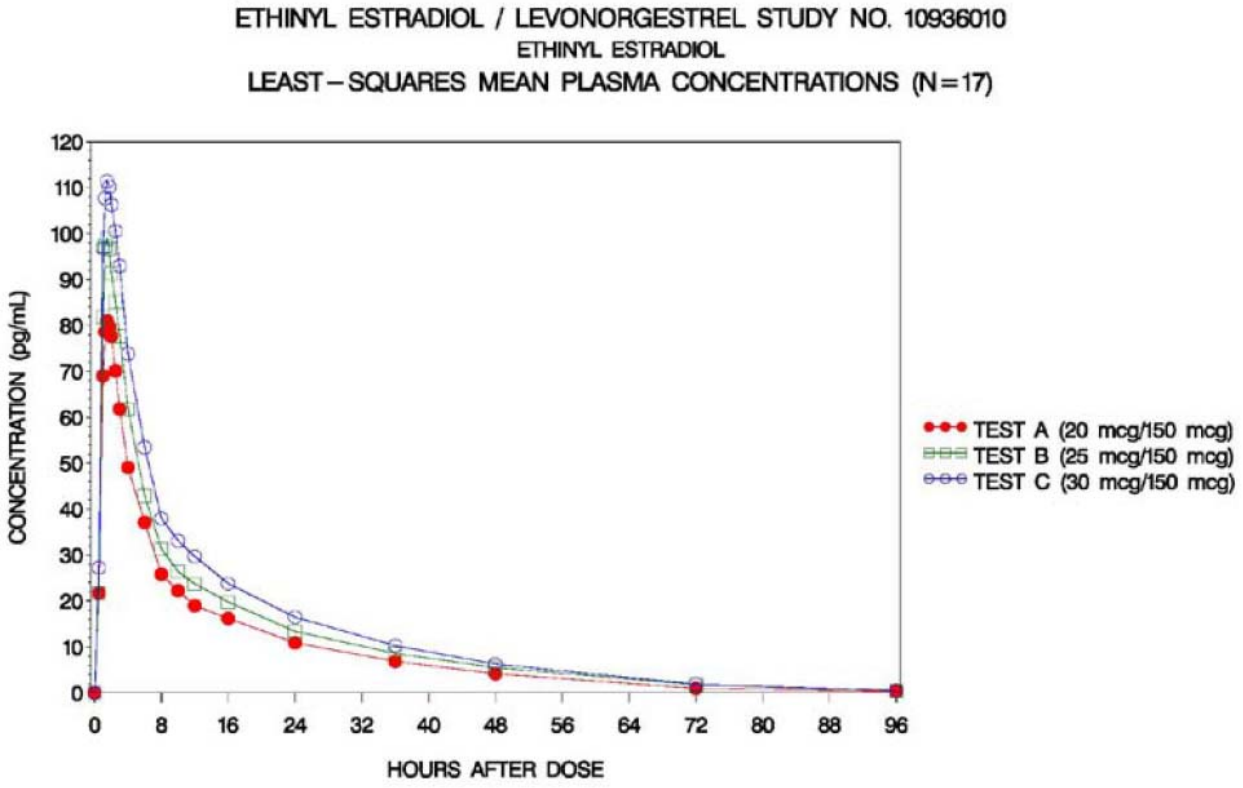


Table 4.2.6. Mean (±SD) PK Parameters of EE

Summary of Pharmacokinetic Parameters
Untransformed Data
Analyte: Ethinyl Estradiol (N = 17)

Pharmacokinetic Parameter	Arithmetic mean ± SD (%CV)		
	Test A	Test B	Test C*
AUC0-t (pg.hr/mL)	864.0218 ± 317.4670 (36.7429)	1085.3753 ± 377.5990 (34.7897)	1312.1113 ± 408.6293 (31.1429)
AUC0-inf (pg.hr/mL)	939.1852 ± 327.0875 (34.8267)	1166.0825 ± 393.2429 (33.7234)	1409.6321 ± 434.4092 (30.8172)
Cmax (pg/mL)	85.8471 ± 25.0501 (29.1799)	105.7353 ± 28.6858 (27.1298)	122.9688 ± 30.7610 (25.0153)
Tmax (hr)	1.5882 ± 0.3638 (22.9061)	1.6912 ± 0.4803 (28.4010)	1.6250 ± 0.4378 (26.9414)
Kel (1/hr)	0.0437 ± 0.0096 (21.9147)	0.0410 ± 0.0112 (27.2713)	0.0428 ± 0.0115 (26.9669)
Elimhalf (hr)	16.7150 ± 4.4107 (26.3875)	18.0962 ± 4.8164 (26.6157)	17.3577 ± 4.9386 (28.4520)

*N=16 for all pharmacokinetic parameters for Test C.

Reference ID: 3265296

Table 4.2.7. Statistical Data of EE

Statistical Comparisons
Analyte: Ethinyl Estradiol (N = 17)

	Test A	Test B	Test C**
Median Tmax (hour)	1.50	1.50	1.50
AUC0-t/AUC0-inf ratio*	0.9200	0.9308	0.9299

*Ratio calculated as AUC0-t LSmean divided by AUC0-inf LSmean.
**N=16 for all pharmacokinetic parameters for Test C.

Table 4.2.8. Statistical Data of EE

Test B versus Test A

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Ethinyl Estradiol (N = 17)

Parameter	Test B	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1031.17	815.56	1.2644	1.2001 - 1.3321	8.0419
AUC0-inf (pg.hr/mL)	1110.77	891.91	1.2454	1.1899 - 1.3035	6.9479
Cmax (pg/mL)	102.11	82.24	1.2415	1.1639 - 1.3244	10.2866

Table 4.2.9. Statistical Data of EE

Test C versus Test A

Geometric Means, Ratio of Means, and 90% Confidence Intervals
Based on ANOVA of Ln-Transformed Data
Analyte: Ethinyl Estradiol (N = 17)

Parameter	Test C*	Test A	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1229.77	815.56	1.5079	1.4312 - 1.5887	9.8496
AUC0-inf (pg.hr/mL)	1325.93	891.91	1.4866	1.4204 - 1.5560	9.1979
Cmax (pg/mL)	114.76	82.24	1.3954	1.3081 - 1.4885	11.0593

*N=16 for all pharmacokinetic parameters for Test C.

Reference ID: 3265296

Table 4.2.10. Statistical Data of EE

Test B versus Test C

Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Ln-Transformed Data Analyte: Ethinyl Estradiol (N = 17)

Parameter	Test B	Test C*	Ratio	CI	Intra-Subject %CV
AUC0-t (pg.hr/mL)	1031.17	1229.77	0.8385	0.7959 - 0.8834	8.0961
AUC0-inf (pg.hr/mL)	1110.77	1325.93	0.8377	0.8004 - 0.8768	6.5675
Cmax (pg/mL)	102.11	114.76	0.8898	0.8341 - 0.9492	10.9598

*N=16 for all pharmacokinetic parameters for Test C.

Reviewer's Comments:

The objective of the study is to characterize the PK profiles of LNG and EE in female subjects and to establish dosage-equivalency among the three tablets strengths for each component.

The data demonstrate dosage proportionality for EE and dosage equivalency for LNG among the three tablets strengths. The plasma concentration-time profiles of LNG are superimposed following the three tablets. For EE, the concentration increased as expected representing the amount of EE in each tablet.

4.3.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Pharmacometrics Reviewer: Jeffry Florian

Pharmacometrics Team Leader: Yaning Wang

Clinical Pharmacology Reviewer: Sayed Al Habet

Clinical Pharmacology Team Leader: Myong-Jin Kim

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions.

Is the scheduled tiered dose escalation of ethinyl estradiol (EE)/ levonorgestrel (LNG) supported by the sponsor's Phase 2b data (DR-ASC-201)?

The sponsor evaluated three ascending dose regimens in DR-ASC-201 (listed below):

Low dose (n=140, at least one complete cycle n=110):

- 42 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 21 days combination active tablets (25 mcg EE/150 mcg LNG) followed by;
- 21 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;
- 7 days of 10 mcg EE tablets.

Midrange dose (n=136, at least one complete cycle n=110):

- 21 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 42 days combination active tablets (25 mcg EE/ 150 mcg LNG) followed by;
- 21 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;
- 7 days of 10 mcg EE tablets.

High dose (n=143, at least one complete cycle n=108):

- 21 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 21 days combination active tablets (25 mcg EE/150 mcg LNG) followed by;
- 42 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;
- 7 days of 10 mcg EE tablets.

Over 2 91-day cycles, there was no distinct difference in the incidence of bleeding or spotting, adverse events, or laboratory parameters between any of the above ascending dose regimens. From a safety perspective, the regimen providing the lowest total cumulative exposure (low dose) was most appropriate for further evaluation in Phase III.

Reference ID: 3265296

One concern with pursuing the low dose arm (or any of the other two ascending dose arms) is the impact lower EE exposures may have on pearl index, the primary endpoint in oral contraception trials. This endpoint requires evaluations over many additional cycles (and patients) and was not included in this trial. However, there are already approved oral contraceptive regimens that utilizes lower and higher doses than those evaluated in this study (Seasonique: 30 mcg EE/150 mcg LNG; over 84-days followed by placebo over 7-days; LoSeasonique: 20 mcg EE/100 mcg LNG over 84 days followed by 10 mcg EE over 7 days), which are predicted to have exposures above and below, respectively, the exposures of the 20 mcg EE/150 mcg LNG (and other) ascending dose arms.

The pharmacokinetic information provided by the sponsor demonstrates that administration of 2 x 20 mcg EE/150 mcg LNG, 2 x 25 mcg EE/150 mcg LNG, and 2 x 30 mcg EE/150 mcg LNG results in dose proportional increases of the EE component. No single dose information on the product was provided; however, if the exposures for administration of a single tablet (i.e., 1 x 20 mcg EE/150 mcg LNG, 1 x 25 mcg EE/150 mcg LNG, 1 x 30 mcg EE//150 mcg LNG) are also dose proportional to the pharmacokinetics observed from administration of two tablets, than the EE exposures for this product will fall between that of two already approved oral contraceptives (Seasonique and LoSeasonique). No comparison of the levonorgestrel pharmacokinetics from the proposed product to previous products were conducted, however, the proposed product has LNG dosing that is equivalent to Seasonique over 84 days and 50% greater than the LNG dosing for LoSeasonique over 84 days.

Overall, the sponsor's selection of the lowest ascending dose arm for further evaluation in Phase III is acceptable. There was no clear difference in safety or bleeding and spotting between the ascending dose arms to support an individual regimen. The EE exposure for all three ascending dose regimens is predicted to be between that of two already approved regimens. Finally, while no comparison of LNG PK between the proposed product and previously approved products was performed, the LNG dose was similar or greater than that used in the already approved products.

Recommendations

The application is approvable from a clinical pharmacology perspective. The available PK data for the ascending dose regimen evaluated in Phase III predicts EE exposures within that of two already approved regimens. A comparison between LNG exposures was not performed; however, the LNG dose in the current product is equivalent to or greater than that of already approved products.

Label Statements

12.3 Pharmacokinetics

(b) (4)

PERTINENT REGULATORY BACKGROUND

DR-103 is a combination estrogen-progestin oral contraceptive intended for the prevention of pregnancy. DR-103 is dosed in a 91-day extended regimen with a triphasic, ascending dose of estrogen (ethinyl estrogen [EE]) combined with a monophasic dose of progestin (levonorgestrel [LNG]):

- 42 days of 0.15 mg LNG/ 0.02 mg EE followed by
- 21 days of 0.15 mg LNG/ 0.025mg EE followed by
- 21 days of 0.15 mg LNG/ 0.03 mg EE followed by
- 7 days of 0.01 mg EE monotherapy during the traditional hormone-free interval.

Data from the following marketed extended-cycle oral contraceptives were used to support characterization of EE PK from DR-103 in the current NDA submission: Seasonale (NDA 21-544), Seasonique (NDA 21-840), and LoSeasonique (NDA 22-262).

RESULTS OF SPONSOR'S ANALYSIS

Introduction

The applicant included a population PK modeling combining EE data from three previous NDAs and a bioequivalence study of DR-103 to characterize PK (dose-proportionality, interindividual variability, single versus multiple dose PK) of the EE component at various formulation

strengths. The applicant selected a regimen for evaluation in Phase III based on safety information from a Phase II dose-ranging study (DR-ASC-201).

Population PK Analysis of Ethinyl Estradiol Concentrations

Report study-cp-12-001.pdf, SBN 000: Population Pharmacokinetic Analysis of Ethinyl Estradiol Concentrations Following Extended-Cycle Oral Contraceptive Regimens and an Assessment of Bleeding Patterns Associated with Different 91-Day Ethinyl Estradiol Dosing Regimens

Datasets

Data for the PK analysis of EE concentrations were obtained from 152 patients enrolled in 5 single-dose studies and 1 multiple-dose study of tablets containing 20 mcg, 25 mcg, or 30 mcg of EE, either alone (study R00-570) or in combination with 150 mcg of levonorgestrel (LNG) (studies 10936010, 10416204, 10216207, 99027, and 99028) (Table 1). Data for the analysis of bleeding and spotting were obtained from 4730 patients enrolled in Phase 3 trials including DR-103 (study DR-103-301), Seasonique (study DR-PSE-301), and LoSeasonique (DR-PSE-309). For the PK analysis of EE concentrations, single EE doses of 30 mcg, 40 mcg (2×20 mcg tablets), 50 mcg (2×25 mcg tablets), or 60 mcg (2×30 mcg tablets); or multiple EE doses of 30 mcg once daily were studied.

The studies included in the PK analysis used intensive sampling strategies from predose to 96 hours after the dose for the determination of plasma EE concentrations. In addition, in study 10216207, trough samples were collected on days 18, 19, 20, 81, 82, and 83 prior to dosing (Table 2).

Table 1: Studies Included in the Pharmacokinetic Analysis

Study number	Phase	Study title	Patients	Duration of trial
DR-103-101 ((b) (4) study 10936010) DR-103	1	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	18 healthy, non-tobacco using, adult female patients with a normal menstrual cycle; 18 to 45 years old; BMI 18 to 30 kg/m^2	Single dose, 3 periods
(b) (4) study 10216207 Seasonique	NS	The single and steady-state pharmacokinetics of DP3 (0.150/0.030 mg levonorgestrel/ethinyl estradiol) tablets in healthy female volunteers	30 healthy, female adult patients with a normal menstrual cycle; 19 to 51 years old; 119 to 191 lb in weight	91 days of dosing (84 days of LNG/EE; 7 days EE alone)
(b) (4) study 10416204 Seasonique	NS	The relative bioavailability of two 0.150/0.030 levonorgestrel/ethinyl estradiol tablet formulations under fasting conditions[a]	30 healthy, non-tobacco using, female adult patients with a normal menstrual cycle; 19 to 51 years old; BMI 18 to 30 kg/m^2	Single dose crossover
(b) (4) study R00-570 Seasonique	NS	A randomized, two-way crossover, relative bioavailability study of ethinyl estradiol tablets in healthy adult females under fasting conditions[b]	18 healthy female patients; 18 to 47 years old; 53 to 87 kg in weight	Single dose crossover
(b) (4) study 99027 LoSeasonique	NS	Randomized, open-label, 2-way crossover, bioequivalence study of (b) (4) (USA) and (b) (4) (USA) Levlite™ levonorgestrel-ethinyl estradiol 0.10 mg-0.02 mg tablets administered as 3 × 0.10 mg-0.02 mg tablets in healthy adult females under fasting conditions	35 healthy, adult female patients with a regular menstrual cycle; 18 to 35 years old; 48 to 75 kg in weight	Single dose crossover
(b) (4) study 99028 Seasonale	NS	Randomized, 3-way crossover, bioequivalence study of (b) (4) (b) (4) (USA) levonorgestrel-ethinyl estradiol 0.15-mg - 0.03-mg tablets and (b) (4) (USA) Nordette® 0.15-mg - 0.03-mg tablets and (b) (4) (b) (4) Min-Ovral® 0.15-mg - 0.03-mg tablets administered as 2 × 0.15-mg - 0.03-mg tablets in healthy adult females under fasting conditions	30 healthy female adult patients; 18 to 35 years old; within 15% of their ideal body weight	Single dose crossover

[a] Bioequivalence of the 2 formulations was demonstrated; therefore, data from both formulations will be included in the analysis.
[b] Data from the comparator arm (oral solution) will not be used in this analysis.
BMI = body mass index; EE = ethinyl estradiol; LNG = levonorgestrel; NS = not stated in study report.

Source: Sponsor's study-cp-12-001.pdf, pg 20

Reference ID: 3265296

Table 2: Dosing Regimens and Pharmacokinetic Sampling Plans of Studies Included in the Pharmacokinetic Analysis

Study number	Phase	Dosing regimen	Pharmacokinetic sampling plan
DR-103-101 (b) (4) study 10936010) DR-103	1	Single increasing dose; 3-period; 10-hour fast before dose; 28 days between doses; 2 tablets per dose Tablet strengths: period 1: levonorgestrel 0.15 mg / ethinyl estradiol 0.020 mg period 2: levonorgestrel 0.15 mg / ethinyl estradiol 0.025 mg period 3: levonorgestrel 0.15 mg / ethinyl estradiol 0.030 mg	Predose (0) and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dose
(b) (4) study 10216207 Seasonique	NS	Multiple dose, 1 period; 1 group; 10-hour fast before doses on day 1, 21, 84, and 91; 1 tablet per dose Tablet strengths: days 1 through 84: levonorgestrel 0.15 mg / ethinyl estradiol 0.030 mg days 85 through 91: ethinyl estradiol 0.030 mg	Days 1, 21: predose (0) and at 0.5, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 11, 15, and 24 hours after dose Days 18, 19, 20, 81, 82, 83: predose Day 84: predose (0) and at 0.5, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 11, 15, 24, 36, 48, 72, 96, 120, and 144 hours after dose Day 91: predose (0) and at 0.5, 1, 1.33, 1.67, 2, 3, 4, 6, 8, 11, 15, 24, 36, 48, 72, and 96 hours after dose
(b) (4) study 10416204 Seasonique	NS	Single dose; 2-way crossover; 10-hour fast before dose; 14 days between doses; 2 formulations; 2 tablets per dose Tablet strength: levonorgestrel 0.15 mg / ethinyl estradiol 0.030 mg	Predose (0) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after dose (EE and LNG) 96 and 120 hours after dose (LNG only)
(b) (4) study R00-570 Seasonique	NS	Single dose; 2-way crossover; 10-hour fast before dose; 28 days between doses; 2 formulations Formulations: ethinyl estradiol tablet 0.030 mg ethinyl estradiol oral solution 0.030 mg / 5 mL	Predose (0) and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dose
(b) (4) study 99027 LoSeasonique	NS	Single dose; 2-way crossover; 10-hour fast before dose; 28 days between doses; 3 tablets per dose Tablet strength: levonorgestrel 0.10 mg / ethinyl estradiol 0.020 mg	Predose (0) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dose
(b) (4) study 99028 Seasonale	NS	Single dose; 3-way crossover; 10-hour fast before dose; 28 days between doses; 3 formulations; 2 tablets per dose Tablet strength: levonorgestrel 0.15 mg / ethinyl estradiol 0.030 mg	Predose (0) and at 0.5, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dose

EE = ethinyl estradiol; LNG = levonorgestrel; NS = not stated in study report.

Source: Sponsor's study-cp-12-001.pdf, pg 22

The dataset used in the population PK modeling included subjects from the treatment arms referenced in the tables above with 1 exception: study R00-570 compared a tablet formulation with an oral solution; the PK data obtained following administration of the oral solution were not included in the analysis dataset.

Table 3: Summary of Demographic Characteristics for the Population Pharmacokinetic Analysis Dataset

Patient characteristic	Statistics	Overall
Age (years)	Mean (SD)	28.32 (7.66)
	Median	28.00
	Min, Max	18.0, 51.0
	n	152
Body mass index (kg/m^2)	Mean (SD)	20.92 (3.59)
	Median	19.90
	Min, Max	15.5, 29.8
	n	152
Weight (kg)	Mean (SD)	65.85 (9.44)
	Median	65.10
	Min, Max	48.2, 88.6
	n	152
Race, n (%)	Caucasian	80 (52.6)
	Black	33 (21.7)
	Hispanic	36 (23.7)
	Other	3 (2.0)
Smoker, n (%)	No	137 (90.1)
	Yes	15 (9.9)

Max = maximum; Min = minimum; n = number of patients; SD = standard deviation.

Source: Sponsor's study-cp-12-001.pdf, pg 36

Methods

The general procedure followed for the development of the PK model is described below.

Exploratory Data Analysis

Exploratory data analyses and data visualization techniques were used to understand the informational content of the dataset with respect to the anticipated model, to search for extreme values and potential outliers, to assess possible trends in the data, and to determine if any errors were made in the manipulation of the data and creation of the analysis datasets.

Base Structural Model Development

Results of the exploratory analyses were used to determine the appropriate functional form of the base structural model. Preliminary examination of plasma EE concentrations suggested that the data would be adequately described by a linear 2-compartment open model with first-order absorption and elimination.

Given that all of the data used in these analyses were obtained following oral administration, the bioavailability fraction (F1) was assumed to be 100% and the PK parameters are considered apparent values. The effect of product was evaluated as a shift in the relative bioavailability fraction as compared to DR-103. After the effect of product was evaluated, the effect of dose on the EE apparent oral clearance (CL/F) was tested prior to the start of the covariate selection process.

Interindividual variability (IIV) in parameters was initially estimated using an exponential error model. Residual variability (RV), representing a composite of assay variability, intraindividual variability, model misspecification, patient noncompliance, and errors in the data, was modeled using a combined additive plus constant coefficient of variation error model.

Covariate Analysis

The potential for selected covariates to explain variability in the dose–plasma concentration relationship for EE was explored. The following stationary demographic and clinical covariates were determined at the screening visit and were assumed to have remained constant for the duration of the study: race, age, weight, body mass index, and smoking. In addition, the effects of product on bioavailability, dose, and single- versus multiple-dose regimens on the PK of EE were investigated.

Covariate analyses exploring the influence of selected factors on the magnitude of IIV and RV in EE PK were performed. The forward selection followed by backward elimination approach for covariate evaluation was used. The covariates described above were evaluated for their ability to explain IIV in CL, V_c, Q, and V_P.

To avoid potential multicollinearity or confounding of effects in covariate submodels, the correlation between covariates was examined. If covariates were found to be highly correlated with other covariates (for example, body weight and BMI), only 1 of the highly correlated

Reference ID: 3265296

covariates was selected for evaluation based on the likelihood of a mechanistic relationship with a parameter or the degree of correlation with a parameter based on univariate analyses. Continuous and categorical covariates were evaluated in NONMEM using linear, exponential, power, additive, or proportional shift models, as appropriate.

A univariate analysis of each covariate was performed using NONMEM. Covariates contributing a change in the VOF of at least 3.84 ($\alpha = 0.05$, 1 df) and resulting in a decrease in IIV in the parameter of interest were considered significant. After the initial univariate analyses were completed, the covariate contributing the most significant change in the VOF (smallest $p < 0.05$) was included in the base covariate model. The new base covariate model (structural model plus 1 significant covariate) was then used to generate new Bayesian estimates of the parameters and to recompute the changes in the parameters.

The error models for IIV and RV in the full multivariable model were evaluated following completion of forward selection. This included the possible addition of new IIV terms to other parameters in the model, evaluation of the appropriateness of the functional form for each IIV term and for the RV model, and assessment of possible correlations between η variables.

Univariate stepwise backward elimination proceeded after all adjustments had been made to the IIV and RV error models. Each covariate was removed from each parameter equation separately. A covariate was considered significant if it resulted in a change in the VOF of at least 10.83 (α=0.001, 1 df for χ^2-distribution) when removed from the model. The most nonsignificant covariate (the highest $p > 0.001$) was removed from the model first and this reduced model then served as the new base multivariable model. The backward elimination procedure was repeated until all remaining covariates were significant at α=0.001.

The final model was used to simulate 1000 replicates of the analysis dataset with NONMEM. Statistics of interest were calculated from the simulated and observed data for comparison; for example, the 5th, 50th (median), and 95th percentiles of the distributions of concentration. These percentiles were then plotted versus time, with the original observed dataset and/or percentiles based on the observed data overlaid to visually assess concordance between the model-based simulated data and the observed data.

Using the final population PK model, EE concentrations were simulated over two 91-day cycles for DR-103, Seasonique, and LoSeasonique based on the dosing regimens used for each product in the Phase 3 trials. Full profiles were simulated on days 1, 42, 63, 84,
and 91 of each cycle and trough samples (prior to dosing) were simulated on all other days. Although the dataset used for model development contained multiple dosing data from Seasonique only, the multiple-dosing shift on Vc and CL was assumed to similarly apply to all products for the purpose of the simulations.

Results

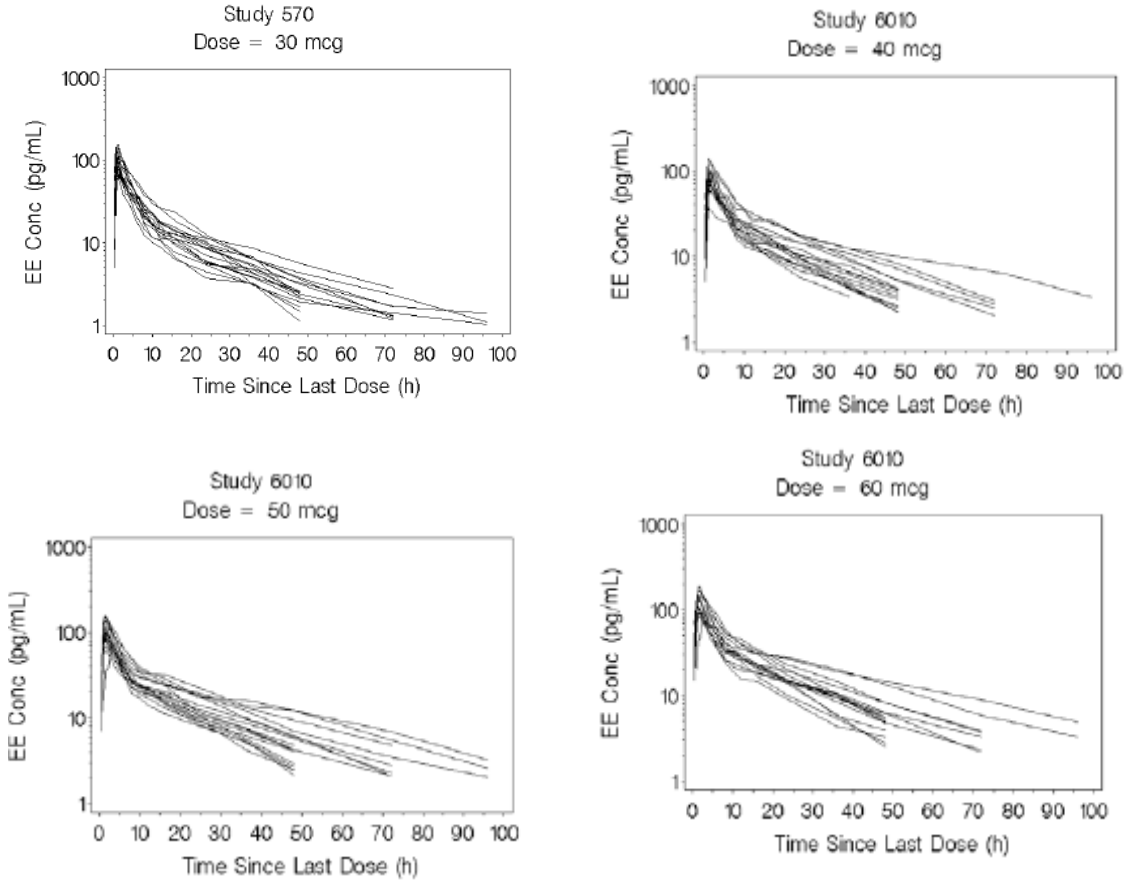
Exploratory Data Analysis

Ethinyl estradiol concentrations versus time profiles, stratified by study, dose, and day (where appropriate), are shown in Figure 1 through Figure 4. Examination of the PK profiles suggested

Reference ID: 3265296

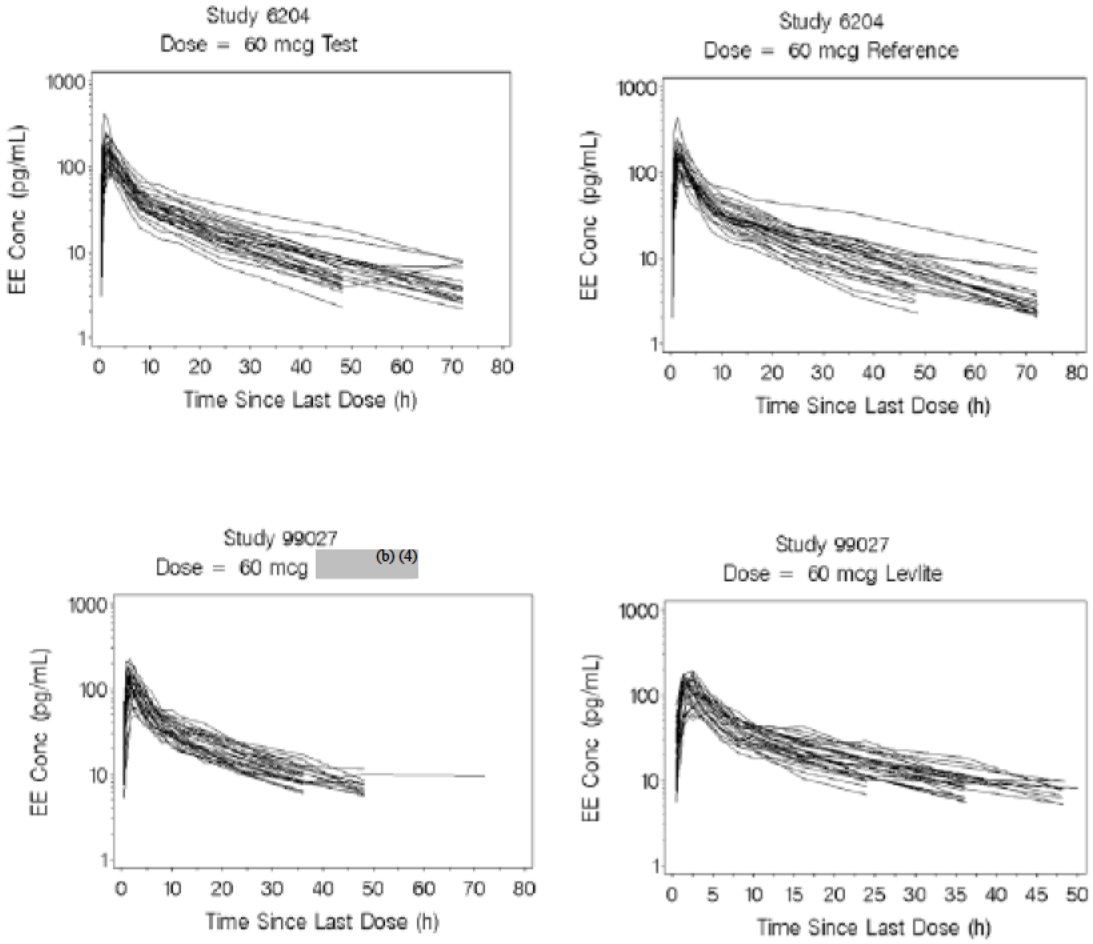
that a linear 2-compartment model would be adequate to describe the concentrationtime course for EE.

Figure 1: Ethinyl Estradiol Concentrations Versus Time Since Last Dose for Study 570 and 6010



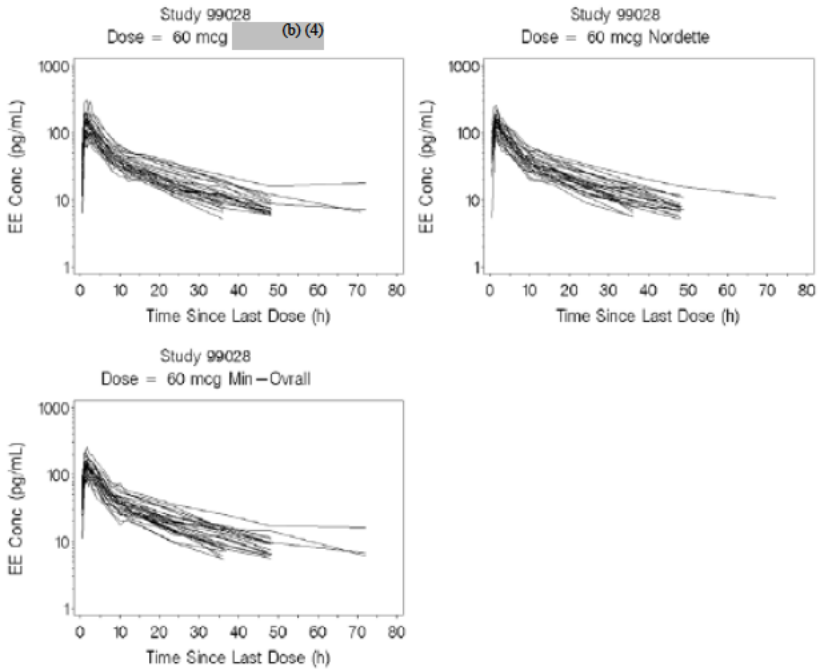
Source: Sponsor's study-cp-12-001.pdf, pg 42-43

Figure 2: Ethinyl Estradiol Concentrations Versus Time Since Last Dose for Study 6204 and 99027



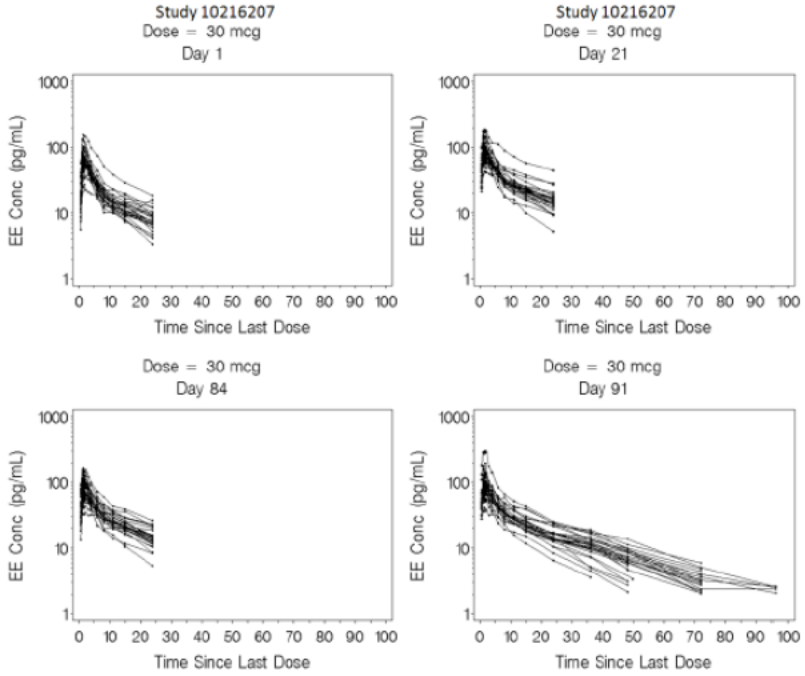
Source: Sponsor's study-cp-12-001.pdf, pg 44

Figure 3: Ethinyl Estradiol Concentrations Versus Time Since Last Dose for Study 99028



Source: Sponsor's study-cp-12-001.pdf, pg 45

Figure 4: Ethinyl Estradiol Concentrations Versus Time Since Last Dose for Study 10216207



Source: Sponsor's study-cp-12-001.pdf, pg 46

Population Pharmacokinetic Model

The final population PK model was a 2-compartment open model with first-order elimination. Absorption was modeled as a combination of zero- and first-order processes. Interindividual variability was estimated with an exponential error structure on apparent oral clearance (CL/F), apparent central volume of distribution (V_c/F), apparent peripheral volume of distribution (V_p/F), apparent intercompartmental clearance (Q/F), absorption rate constant (ka), and the duration of zero-order absorption (D1). Residual variability (RV) was expressed as a combination of additive plus constant coefficient of variation error model.

The bioavailability of EE when administered as Seasonique or Seasonale was 1.17 (95% confidence interval; 1.06 to 1.28) relative to the DR-103 or LoSeasonique products (F = 1). The typical values of the PK parameters for EE in the DR-103 formulation were: CL/F (48.1 L/h), V_c/F (368 L), V_p/F (505 L), Q/F (61.0 L/h), ka (1.92 h-1), and D_1 (0.68 h). The magnitude of IIV was small in all parameters, ranging from 25% to 37% CV.

Table 4: Parameter Estimates and Standard Errors from the Final Model

	Final parameter estimate		Magnitude of interindividual variability (%CV)	
Parameter	Population mean	%SEM	Final estimate	%SEM
CL/F (L/h)	48.1	3.7	27.55[c]	12.3
Shift on CL/F (L/h)[a]	-7.8	19.0		
V_c/F (L)	368	4.3	35.21[c]	15.6
Shift on V_c/F (L)[a]	-74.9	15.4		
V_p/F (L)	505	4.1	29.39[c]	12.7
Q/F (L/h)	61.0	4.1	24.52[c]	17.1
K_a (1/h)	1.92	3.6	31.40	23.7
D1 (h)	0.68	3.1	36.88	15.6
F1	1.17	4.6	NE	NA
RV[b]	1.36, 0.163	25.8, 4.4	NA	NA
Minimum value of the objective function = 33182.693				

[a] Additional shift for multiple dosing versus single dose.

[b] Residual variability expressed as standard deviations of the additive and constant coefficient of variation components, respectively. These estimates correspond to a range of residual variability from 69.9 %CV and at an individual predicted EE concentration of 2 pg/mL to 16.3 %CV at an individual predicted EE concentration of 325 pg/mL.

[c] Estimates (%SEM) of covariance terms:
(IIV on CL, IIV on Vc) = 0.0689 (16.3%)
(IIV on CL, IIV on Q) = 0.0478 (17.8%)
(IIV on Vc, IIV on Q) = 0.0558 (19.0%)
(IIV on CL, IIV on Vp) = 0.0472 (18.0%)
(IIV on Vc, IIV on Vp) = 0.0487 (20.7%)
(IIV on Q, IIV on Vp) = 0.0690 (14.8%)

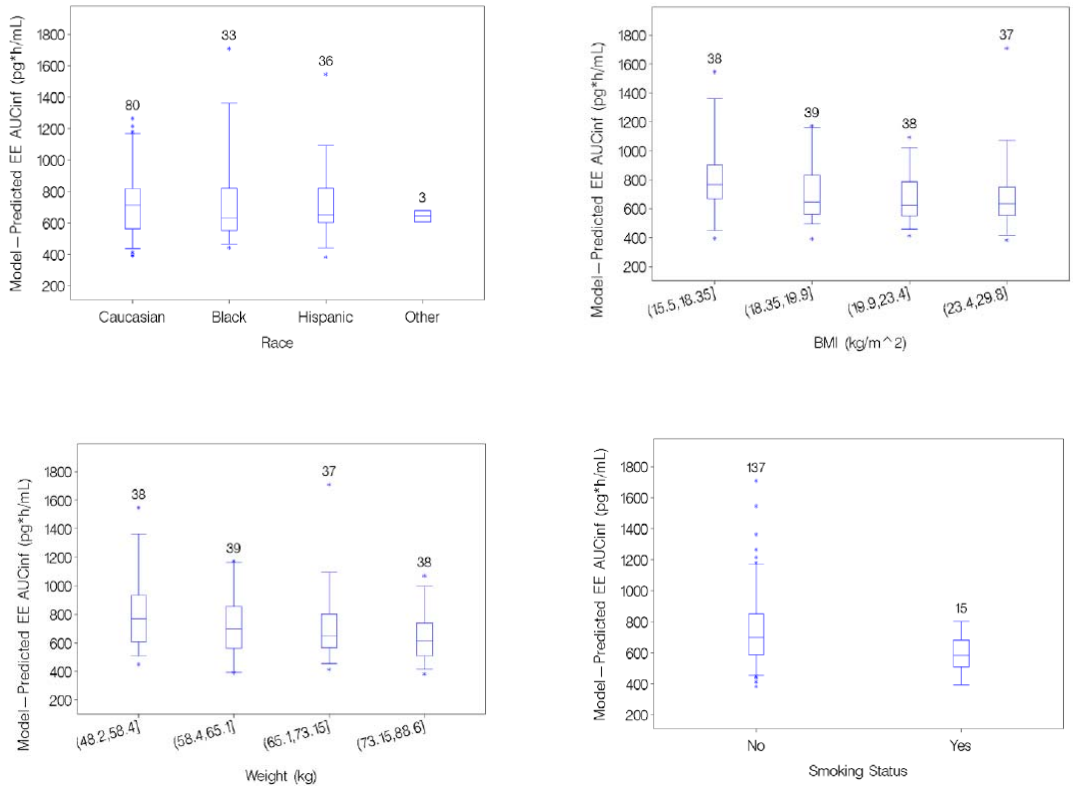
CL/F = apparent oral clearance; D1 = duration of zero-order input into absorption (depot) compartment; F1 = bioavailability of Seasonique and Seasonale products relative to DR-103 and LoSeasonique; k_a = first-order absorption rate constant; NA = not applicable; NE = not estimated; Q/F = apparent intercompartmental clearance; %SEM = percent standard error of the mean; RV = residual variability; V_c/F = apparent central volume of distribution; V_p/F = apparent volume of the peripheral compartment.

Source: Sponsor's study-cp-12-001.pdf, pg 532

There was a statistically significant reduction in CL (7.8 L/h) and V_c (74.9 L) noted after multiple dosing with EE relative to the PK parameters estimated after the 1st dose. The terminal elimination half-life after a single dose was 16.5 hours; after multiple dosing the half-life was 17.8 hours. The volume of distribution at steady-state was 873 L.

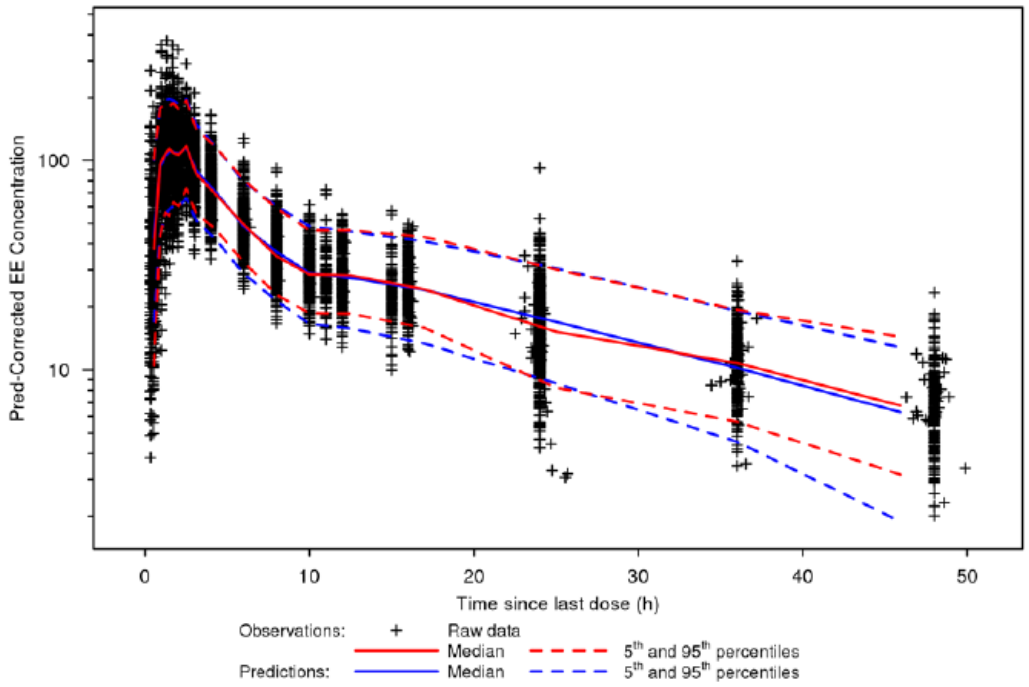
None of the demographic covariates evaluated (race, age, weight, body mass index [BMI], or smoking status) resulted in a statistically significant effect after forward selection ($p > 0.05$) and backward elimination ($p > 0.001$); there was a trend for increased CL, Q, Vc, and Vp with increased body weight. No effect of cigarette smoking could be detected, but only 15 patients were reported to be smokers. A prediction-corrected visual predictive check of the final population pharmacokinetic model for ethinyl estradiol indicates no apparent biases in the overall model fit, with 4.3% and 4.9% of observed concentrations falling below and above the 90% prediction interval, respectively.

Figure 5: Box plots of Model-Predicted EE AUC Versus Race, BMI, Weight, and Smoking



Source: Sponsor's study-cp-12-001.pdf, pg 59

Figure 6: Visual Predictive Check of the Final Model



Source: Sponsor's study-cp-12-001.pdf , pg 52

The population PK model and the final parameter estimates were used to predict daily trough concentrations for the DR-103, Seasonique, and LoSeasonique dosing regimens in the Phase 3 studies. The predicted EE trough concentrations for the DR-103 product on the day prior to the programmed change in EE dose over the extended 91-day cycle were as follows: day 42: 9.67 pg/mL, day 63: 12.08 pg/mL, day 84: 14.50 pg/mL, and day 91: 4.85 pg/mL. Given the dosing regimens used in the Phase 3 studies, predicted EE trough concentrations for Seasonique were: 16.97 pg/mL on days 42, 63, and 84, and 5.67 pg/mL on day 91, while predicted EE trough concentrations for LoSeasonique were: 9.67 pg/mL on days 42, 63, and 84, and 4.84 pg/mL on day 91.

Table 5: Predicted Ethinyl Estradiol Exposure Measures Based on Simulations of the Dosing Regimens in the DR-103, Seasonique, and LoSeasonique Products

Reference ID: 3265296

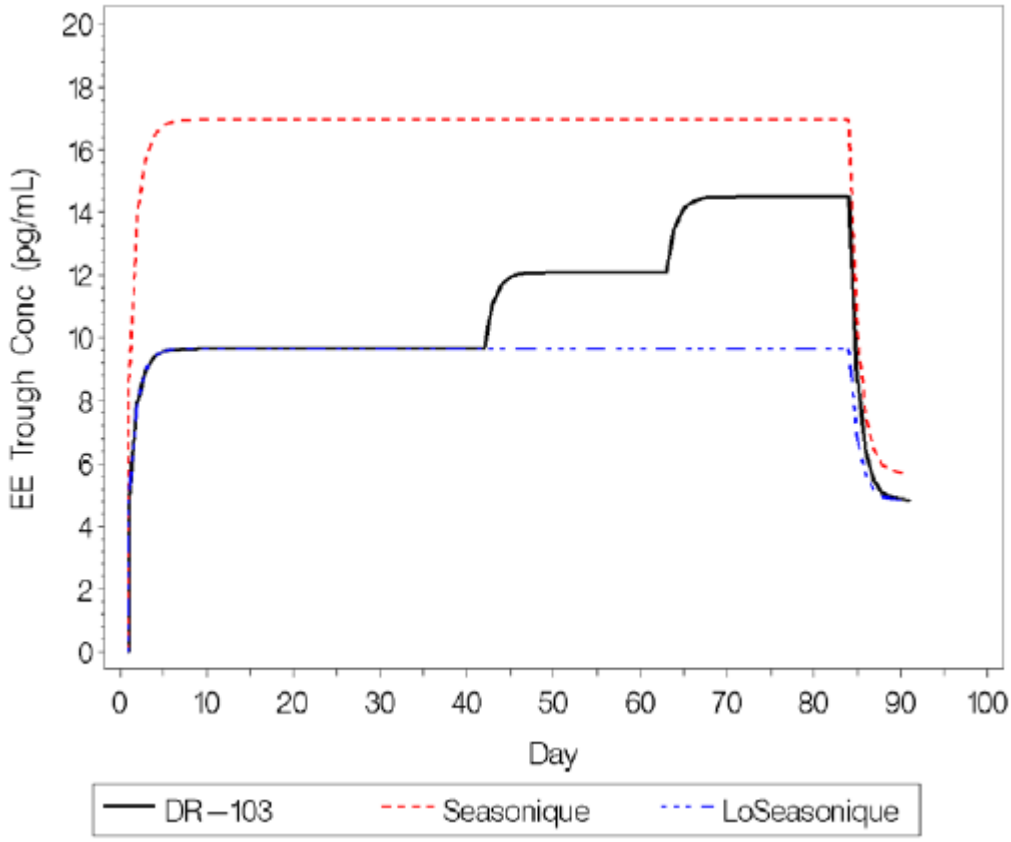
Ethinyl estradiol exposure measure	Day	DR-103	Seasonique	LoSeasonique
AUC_{0-24} (pg×h/mL)	1	303.312	532.312	303.312
	42	499.886	877.291	499.886
	63	624.848	877.291	499.886
	84	749.823	877.291	499.886
	91	250.503	293.088	250.222
C_{max} (pg/mL)	1	38.488	67.546	38.488
	42	55.773	97.882	55.773
	63	69.717	97.882	55.773
	84	83.660	97.882	55.773
	91	27.921	32.667	27.904
C_{min} (pg/mL)	1	4.8610	8.5311	4.8610
	42	9.6665	16.9650	9.6665
	63	12.0830	16.9650	9.6665
	84	14.5000	16.9650	9.6665
	91	4.8474	5.6715	4.8403

AUC_{0-24} = area under the plasma concentration by time curve from time zero to 24 hours at steady state, C_{max} = maximum observed plasma drug concentration; C_{min} = minimum observed plasma drug concentration; Max = maximum; Min = minimum; n = number of patients; PK = pharmacokinetic; SD = standard deviation.

Source: Sponsor's study-cp-12-001.pdf, pg 71

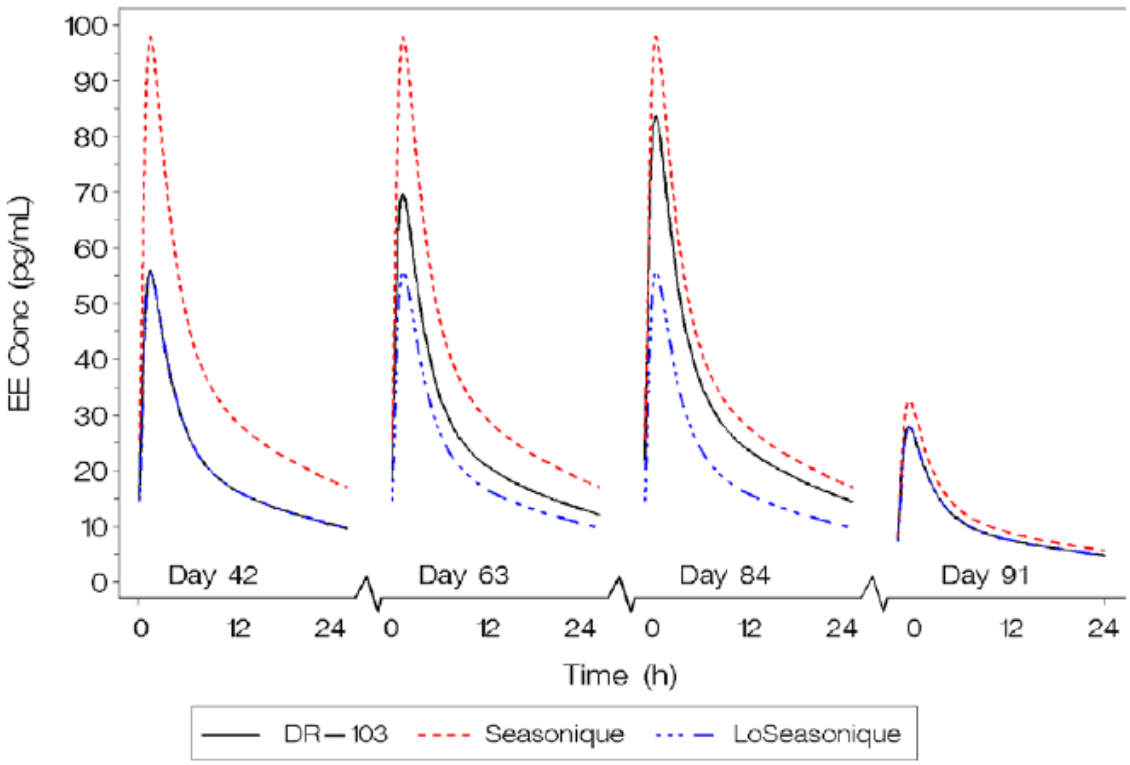
Figure 7: Comparison of Daily-Predicted Ethinyl Estradiol C_{min} Values for the Dosing Regimens in the DR-103, Seasonique, and LoSeasonique Products

Reference ID: 3265296



Source: Sponsor's study-cp-12-001, pg 712

Figure 8: Comparison of Predicted Ethinyl Estradiol Concentrations Over a Dosing Interval on Days 42, 63, 84, and 91 for the DR-103, Seasonique, and LoSeasonique Products



Source: Sponsor's study-cp-12-001, pg 72

Reviewer's Comment: The sponsor developed a population PK model for describing ethinyl estradiol concentrations using single dose data for the current submission (DR-103), single-dose data from previous submissions (Seasonale, Seasonique, and LoSeasonique), and multi-dose data from a previous submission (Seasonique). These studies were performed only in women and included intensive PK sampling.

The population PK model developed by the sponsor identified a difference in model defined bioavailability (F1) between the current formulation (DR-103) and Seasonique or Seasonale based on the single dose data. No significant difference in bioavailability was identified between DR-103 and Lo-Seasonique. The ramification of this difference in bioavailability was simulated for an entire treatment cycle and the predicted differences are depicted in Table 5, Figure 7, and Figure 8).

The sponsor's single dose data predicts that EE exposures of the DR-103 formulation are between the exposures of LoSeasonique and Seasonique for EE doses of 20, 25, and 30 mcg per day. The only actual data for DR-103 comes from administration of 2 x 20, 2 x 25, and 2 x 30, and this analysis assumes that the PK for the EE component will be proportional to what was observed for administration of two tables. The predicted multi-dose effects on clearance and volume of distribution that were observed from Seasonique data may also differ for DR-103 (and LoSeasonique) (only single dose data for these compounds). However, the predicted impact of multiple dosing on EE clearance and volume of distribution are not used for dose adjustment for DR-103 (16.3% decrease in steady-state clearance). This is supported by the labels for

Reference ID: 3265296

Seasonique and LoSeasonique, which, despite these effects with Seasonique (and extrapolated effects for LoSeasonique), no dose adjustments are made for repeated dosing.

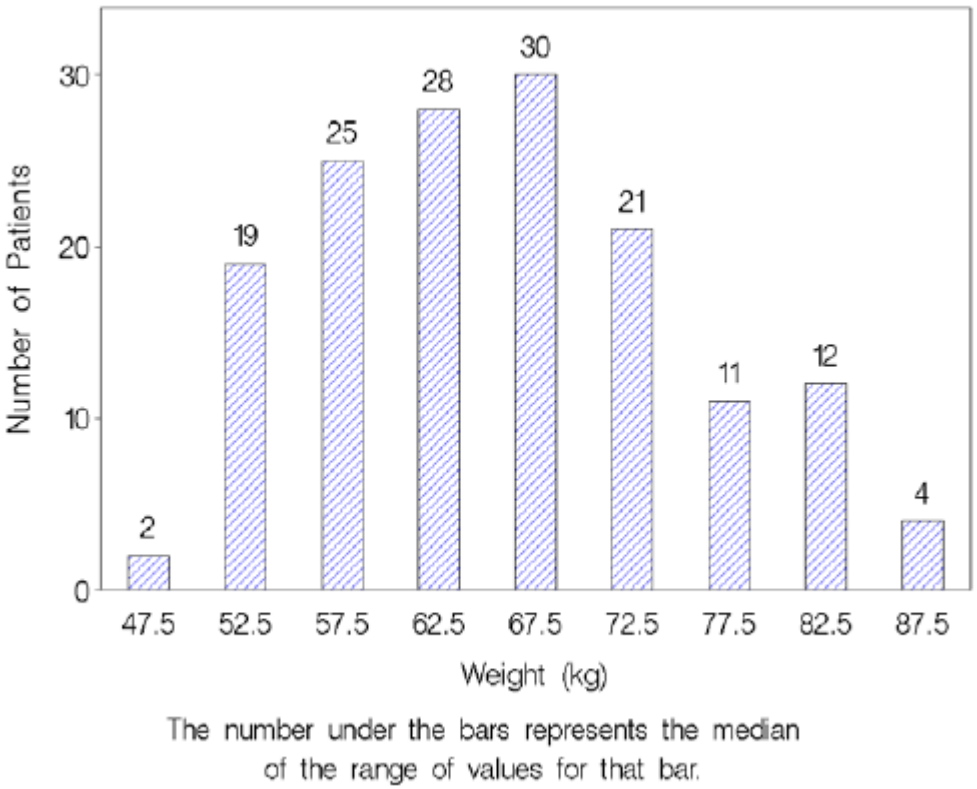
The sponsor was unable to identify significant effects of body weight, body mass index, or smoking on EE pharmacokinetics. However, these results should be interpreted with caution. The mean [min; max] body weight of patients included in this analysis was 65 [48; 89] kg. Less than 10% of the patients had body weight >80 kg, and none of the subjects had body weight >90 kg. Over the range of weights included in the population PK analysis a 25% difference in AUC was predicted between the lowest and highest quartile. In addition, interindividual variability plots for model parameters (CL, V_c, Q, and V_p) demonstrated a trend with respect to body weight. This trend, as well as the increased focus on sensitivity analysis of Phase III data based on body weight (>90 kg) suggests that the available data is insufficient to rule out a body weight effect on EE clearance. The reviewer performed an independent assessment in Section 4 where body weight was included even if the improvement in object function criteria was not satisfied to obtain predictions on the impact of body weight >90 kg on ethinyl estradiol exposures.

Similarly, a difference of 20% was observed between subjects categorized as smokers within the population PK dataset. However, this difference was not identified as significant, possibly due to the small number of non-smokers (n=15) included in the overall dataset.

Overall, the sponsor's conclusion of no significant covariates on EE clearance based on their population PK analysis is correct based on the described methodology. However, the data included in the analysis may not be sufficient to have identified covariate effects due to smoking, and simultaneous addition of covariates may have been necessary in order to identify body weight as a significant covariate during model development.

Figure 9: Frequency Distribution of Weight for Patients Included in the Population Pharmacokinetic Analysis Dataset

Reference ID: 3265296



Source: Sponsor's study-cp-12-001.pdf , pg 52

Dose Ranging Phase 2B Study for DR-103 Treatment

Report 201-ectd-body.pdf, SBN 000: 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

Study Design

The sponsor 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 III. All four treatment regimens consist of combination active tablets containing EE and 150 mcg LNG. The three ascending EE dose regimens utilized 10 mcg EE during the 7-day interval between each 84-day cycle of combination therapy. The fourth arm evaluated Seasonale (30 mcg EE/150 mcg LNG) as an 84-day regimen with placebo over days 85-91 (n=148, at least one complete cycle n=120). The three ascending dose regimens are described below:

Low dose (n=140, at least one complete cycle n=110):

- 42 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 21 days combination active tablets (25 mcg EE/150 mcg LNG) followed by;
- 21 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;

- 7 days of 10 mcg EE tablets.

Midrange dose (n=136, at least one complete cycle n=110):

- 21 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 42 days combination active tablets (25 mcg EE/ 150 mcg LNG) followed by;
- 21 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;
- 7 days of 10 mcg EE tablets.

High dose (n=143, at least one complete cycle n=108):

- 21 days combination active tablets (20 mcg EE /150 mcg LNG) followed by;
- 21 days combination active tablets (25 mcg EE/150 mcg LNG) followed by;
- 42 days combination active tablets (30 mcg EE/ 150 mcg LNG) followed by;
- 7 days of 10 mcg EE tablets.

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).

Results

Summary statistics for the total number of bleeding/spotting (B/S) days during the first 84 days and during days 8-84 (e.g., excluding the first 7 days of each cycle) are shown in Table 6 and Table 7. The percentage of subjects with bleeding/spotting days was similar between all four treatment arms. Both tables show 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 6: 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: Sponsor's 201-ectd-body.pdf, pg 56

Table 7: Excluding first 7 days: Summary Statistics of Total number of B/S days

Reference ID: 3265296

during each active cycle – ITT Cohort

Treatment Groups	Cycle	N	n (%)	Mean (SD)	Min	Median	Max
Low dose	1	110	93 (84.5%)	16.1 (15.67)	0	11	67
	2	107	76 (71%)	9.4 (14.07)	0	5	74
Midrange dose	1	110	88 (80%)	15.6 (14.81)	0	13	65
	2	108	76 (70.4%)	11.1 (13.44)	0	6.5	69
High dose	1	108	91 (84.3%)	18.3 (17.01)	0	13	67
	2	107	73 (68.2%)	9.7 (14.43)	0	3	68
Seasonale®	1	120	104 (86.7%)	15.4 (13.58)	0	13.5	54
	2	119	82 (68.9%)	8.9 (11.21)	0	4	54

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

Source: Sponsor's 201-ectd-body.pdf, pg 57

Total number of bleeding and spotting days during each active cycle was categorized (7 or more days; 14 or more days; 20 or more days) and is summarized in Table 8. Similar to the previous analysis the percentage of subjects categorized by bleeding and spotting days was similar between the 4 treatment arms, and there was a reduction in the number of events between the first and second cycle

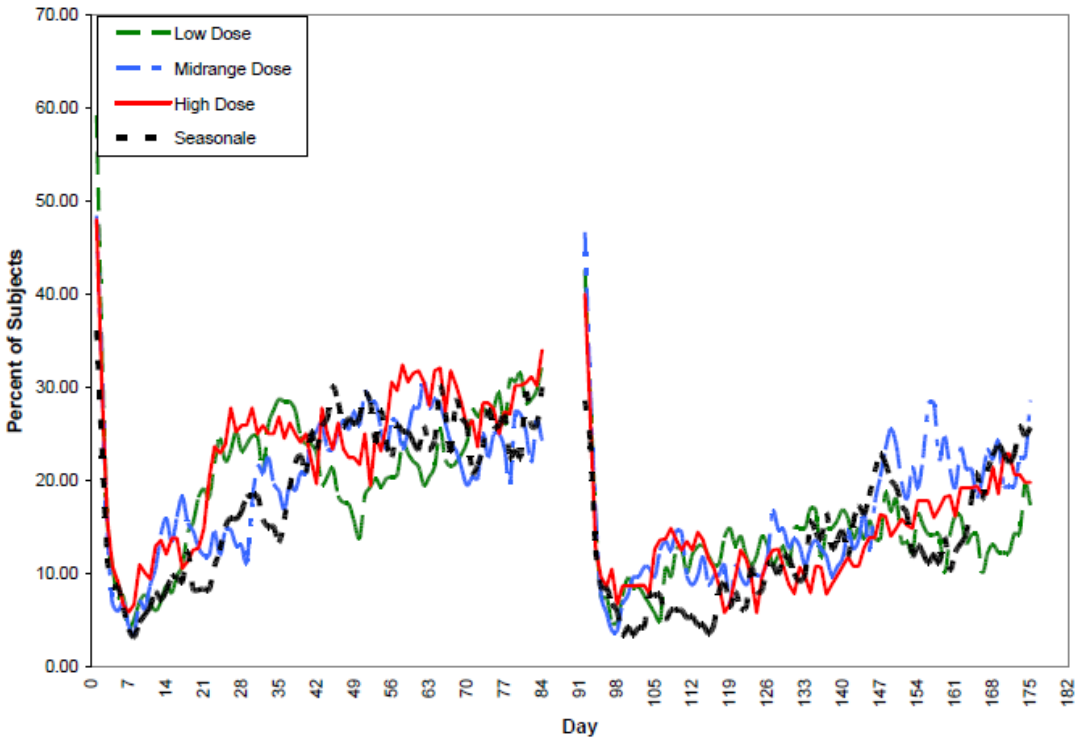
Table 8: Number (Percent) of Subjects with B/S Days during each active cycle – ITT Cohort

	Cycle	Low Dose	Midrange Dose	High Dose	Seasonale®
7 or more days	1	80 (72.73%)	72 (65.45%)	83 (76.85%)	84 (70.00%)
	2	48 (44.04%)	56 (51.85%)	45 (42.06%)	55 (45.83%)
14 or more days	1	53 (48.18%)	55 (50.00%)	55 (50.93%)	64 (53.33%)
	2	26 (23.85%)	38 (35.19%)	25 (23.36%)	33 (27.50%)
20 or more days	1	40 (36.36%)	41 (37.27%)	40 (37.04%)	43 (35.83%)
	2	16 (14.68%)	26 (24.07%)	18 (16.82%)	21 (17.50%)

Source: Sponsor's 201-ectd-body.pdf, pg 58

Figure 10 shows the proportion of subjects with bleeding and spotting events for each treatment over each cycle. No distinct separation in the number of events was observed between any of the treatment arms.

Figure 10: Proportion of subjects with bleeding or spotting during cycle 1 or 2 over the 84-day active cycle



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

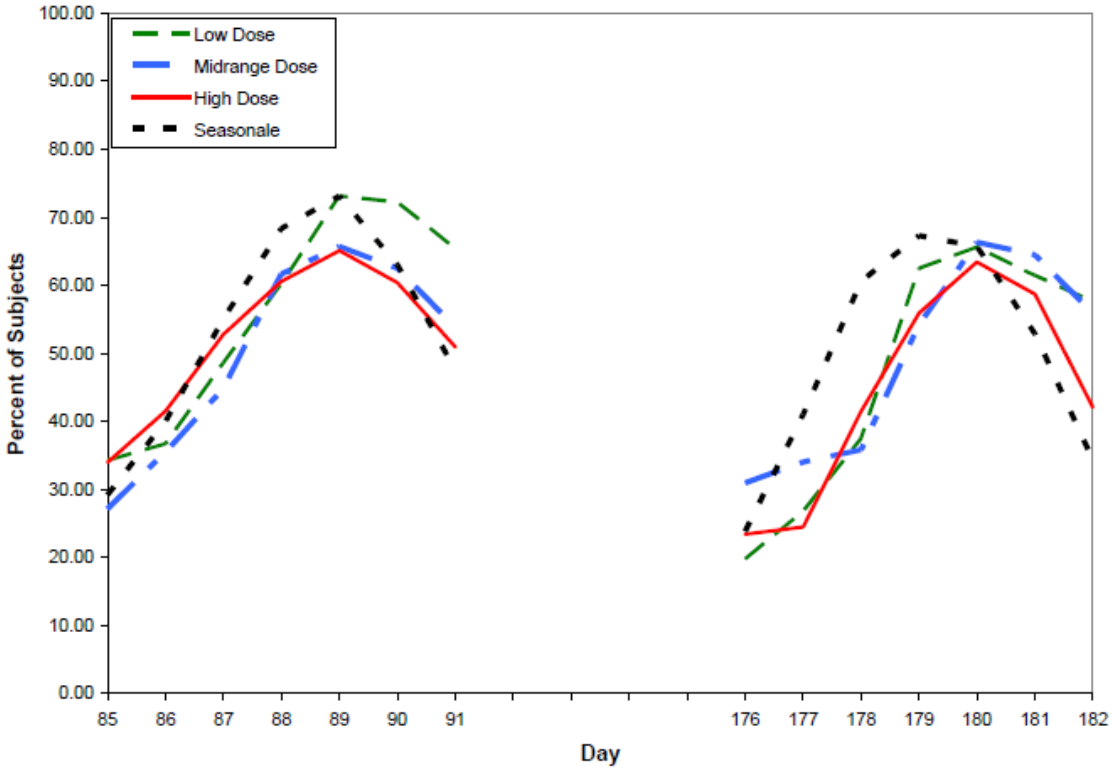
Bleeding and spotting during the 7-day withdrawal cycle are shown below as a categorical analysis (Table 9) and time course (Figure 11). The onset of withdrawal bleeding and spotting appeared to be delayed by 1-2 days for the ascending dose regimens. In addition, fewer patients had 4-7 days of bleeding/spotting on the ascending dose regimens compared to the control arm.

Table 9: Number (Percent) of Subjects with B/S Days during each withdrawal cycle – ITT Cohort

	Cycle	Low Dose	Midrange Dose	High Dose	Seasonale®
0 day	1	14 (12.84%)	28 (25.93%)	25 (23.58%)	27 (22.50%)
	2	15 (15.46%)	20 (20.83%)	23 (24.47%)	21 (20.00%)
1-3 days	1	36 (33.03%)	17 (15.74%)	27 (25.47%)	18 (15.00%)
	2	32 (32.99%)	32 (33.33%)	26 (27.66%)	24 (22.86%)
4-7 days	1	59 (54.13%)	63 (58.33%)	54 (50.94%)	75 (62.50%)
	2	50 (51.55%)	44 (45.83%)	45 (47.87%)	60 (57.14%)

Source: Sponsor's 201-ectd-body.pdf, pg 63

Figure 11: Proportion of subjects with bleeding or spotting during cycle 1 or 2 during 7-day withdrawal cycle



Source: Sponsor's 201-ectd-body.pdf, pg 64

Reviewer's comments: The sponsor selected the ascending low dose regimen for further evaluation in Phase III based on the results of DR-ASC-201. No PK data was collected during this study for relating observed events to measured exposure. The trial consisted of four treatment arms, and the primary focus was on bleeding/spotting events during the treatment cycle and safety events for dosing. All four treatments were observed to have a similar percentage of subjects with bleeding/spotting days. A lower percentage of subjects had 0 days of bleeding/spotting during the withdrawal cycle on the low dose regimen compared to the mid dose arm, high dose arm, and control arm. There was a trend of fewer 4-7 days events during the withdrawal phase for the ascending dose arms than the control arm. The ascending dose treatment arms and the control arm had similar safety.

Overall, there is no definitive distinction in the bleeding/spotting events between the treatment arms. All three treatment arms provide lower cumulative EE dosing compared to the control arm. One concern with pursuing the low dose arm (or any of the other two ascending dose arms) is the impact lower EE doses (and potentially lower EE exposures) may have on pearl index, the primary endpoint in oral contraception trials. This endpoint requires evaluations over many additional cycles and patient and was not included in this trial. However, there is already an approved oral contraceptive regimen that utilizes lower doses than those evaluated in this study (LoSeasonique: 20 mcg EE/100 mcg LNG over 84 days followed by 10 mcg EE over 7

days). The population PK analysis predicts that the EE exposures for DR-103 20 mcg EE/150 mcg LNG will be similar to that of LoSeaonique 20 mcg EE/100 mcg LNG assuming the administration of a single table of DR-103 is proportional to administration of two tablets (see above Reviewer comment). As there are two approved oral contraceptives with EE exposures predicted to bracket that of all three ascending dose arms, the LNG dosing in the ascending dose is similar or greater than that in already approved regimens, and there is no clear difference in safety or bleeding and spotting between the ascending dose arms, the sponsor's selection of the lowest ascending dose arm for further evaluation in Phase III is acceptable.

REVIEWER'S ANALYSIS

Introduction

The final population pharmacokinetic model developed by the sponsor included two compartments, a multidose effect on clearance and volume of distribution, but no significant impact of body weight on any of the model parameters. However, the interindividual variability plots for CL, V_d, Q, and V_p displayed trends with respect to body weight. In addition, there was a difference of 25% in AUC_{ss} between the 1st and 4th body weight quartile in the population PK dataset. Finally, the body weight range included in the sponsor's population PK analysis included no subjects with body weight >90 kg. In order to obtain predictions of the impact on body weight in subjects with body weight >90 kg the reviewer performed an independent population pharmacokinetic analysis based on the model structure identified by the sponsor.
In addition, race and body weight were identified as demographic factors associated with treatment effect in the Phase III single arm study (DR-301). As race and body weight were related, a sensitivity analysis was performed by the reviewer to determine if body weight remained a predictive factor for response after accounting for race.

Objectives

Analysis objectives are:

Extend the sponsor's population pharmacokinetic model to include body weight effects for the purpose of predicting exposures in subjects >90 kg

Evaluate the impact of previously identified demographic factors on Phase III treatment results and determine if body weight remained a factor after accounting for race

Methods

Data Sets

Data for the population pharmacokinetic analysis was identical to that used in the sponsor's analysis described above in Table 1 and Table 2. A demographic summary of these patients is provided in Table 3 and observed ethinyl estradiol concentration versus time profiles for patient data used in this analysis are shown in Figure 1 through Figure 4.

Data sets used are summarized in Table 10. Data from site "LA-0012' was removed from the analysis due to failed site inspection. In addition, three additional subjects were included as having pregnancy occur while on treatment based on the Medical and Statistical Officer's review of the information provided by the sponsor (subject IDs: "DR-103-301-FL-0001-10001115","DR-103-301-MD-0005-10005055","DR-103-301-NC-0042-10042029").

Reference ID: 3265296

Table 10. Analysis Data Sets

Study Number	Name	Link to EDR
d_adeff.xpt, d_adsl.xpt	Analysis datasets for efficacy and subject level data	\\Cdsesub1\evsprod\NDA204061\0005\m5\datasets\dr-103-301\analysis

Software

Diagnostic graphs, model comparison, and statistical analysis were performed in R (version 12.0). Estimation and simulation were performed NONMEM version 7.2 on the Pharmacometrics Group Linux cluster using the front end manager Perl Speaks NONMEM (PsN).

Population Pharmacokinetic Model

The sponsor's final population PK model was used as the starting point for the reviewer's analysis. The structure was a 2-compartment open model with first-order elimination and absorption modeled as a combination of zero- and first-order processes. Interindividual variability was estimated with an exponential error structure on apparent oral clearance (CL/F), apparent central volume of distribution (V_c/F), apparent peripheral volume of distribution (V_p/F), apparent intercompartmental clearance (Q/F), absorption rate constant (ka), and the duration of zero-order absorption (D1). Residual variability was expressed as a combination additive plus constant coefficient of variation error model.

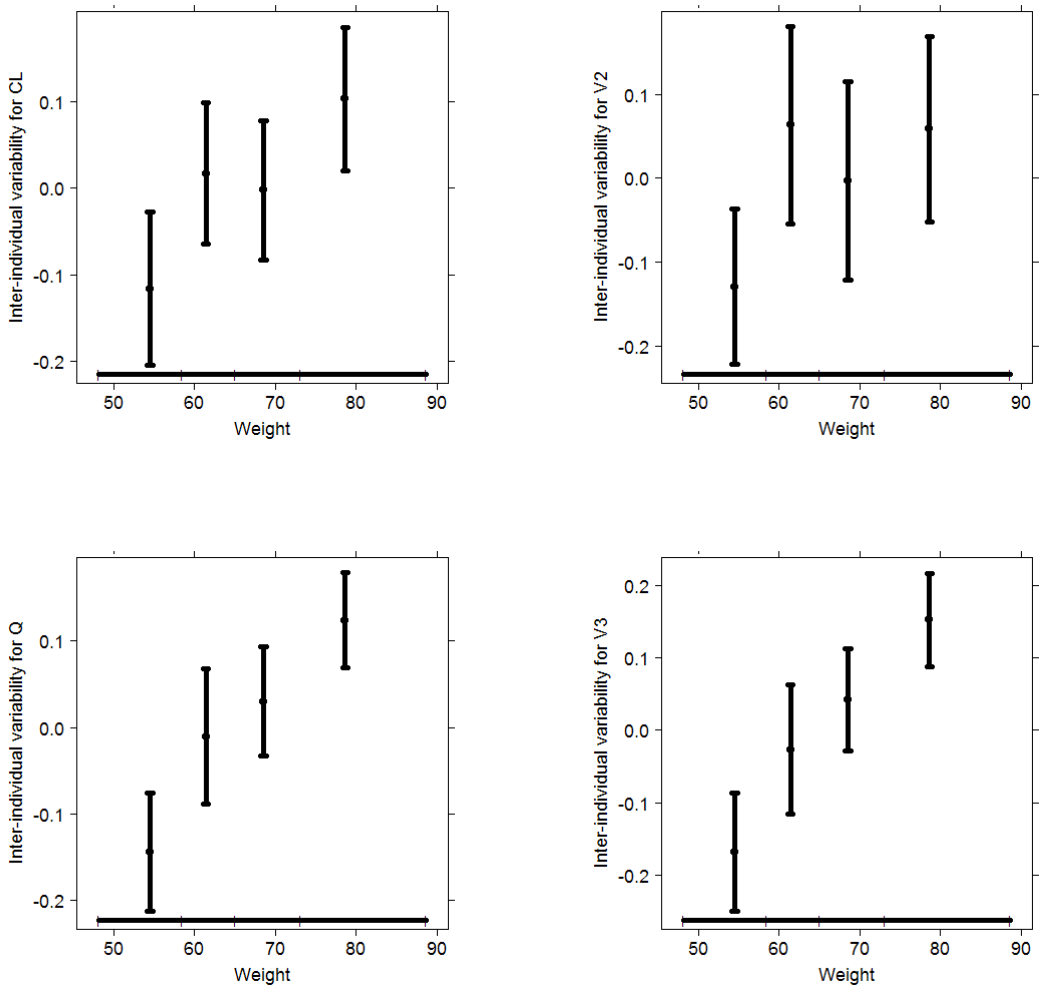
Covariates identified by the sponsor were also included in the reviewer's evaluation. These covariates included the identified parameters for bioavailability based on Seasonique or Seasonale relative to the DR-103 or LoSeasonique. In addition, multidose effects on clearance and volume of distribution were included in the model.

The reviewer's analysis focused on evaluating the impact of body weight on the sponsor's model. In the sponsor's final analysis, body weight was not identified as a significant covariate in the model; however, each model parameter demonstrated a relationship between interindividual variability and body weight in the final model Figure 12.

In the reviewer's analysis, body weight was included as a power-law relationship normalized to a typical body weight of 70 kg. This covariate could be included on CL or V_c individually, or at the same time, though separate parameters were included for CL and V_c. In addition, the reviewer evaluated simultaneous covariate parameterization on CL and Q with one power-law covariate and V_c and V_p with a separate covariate or using a separate power-law covariate on CL, Q, V_c, and V_p. The typical forward stepwise covariate evaluation was not followed because it failed to identify body weight as a significant covariate for these parameters despite a clear relationship as shown in Figure 12. Instead, body weight as included in the covariate model for all four parameters simultaneously. The change of objective function was compared to 18.5 (α = 0.001, 4 df).

Reference ID: 3265296

Figure 12: Interindividual Variability Plots for CL, V_c (V2), Q, and V_p (V3) Versus Body Weight for the Sponsor's Final Model



Pearl Index Calculation

The primary efficacy endpoint for DR-103-301 was the pregnancy rate reported as pearl index (PI) using all pregnancies as determined by a positive urine and/or serum pregnancy test except those for which the date of conception was before starting DR-103 or > 7 days after stopping the combination EE/LNG treatment of DR-103. The sponsor's original analysis included 67 events, and 3 additional events were identified by the review team based on the above criteria.

This independent assessment of PI defined PI as the number of contraceptive failures per 100 women-years of exposure. Formulas are provided below for both the 91-day cycle and the 28-day cycle-equivalent:

- (100) x (total number of pregnancies) x (4)/(total number of 91-day cycles)
- (100) x (total number of pregnancies) x (13)/(total number of 28-day cycles)

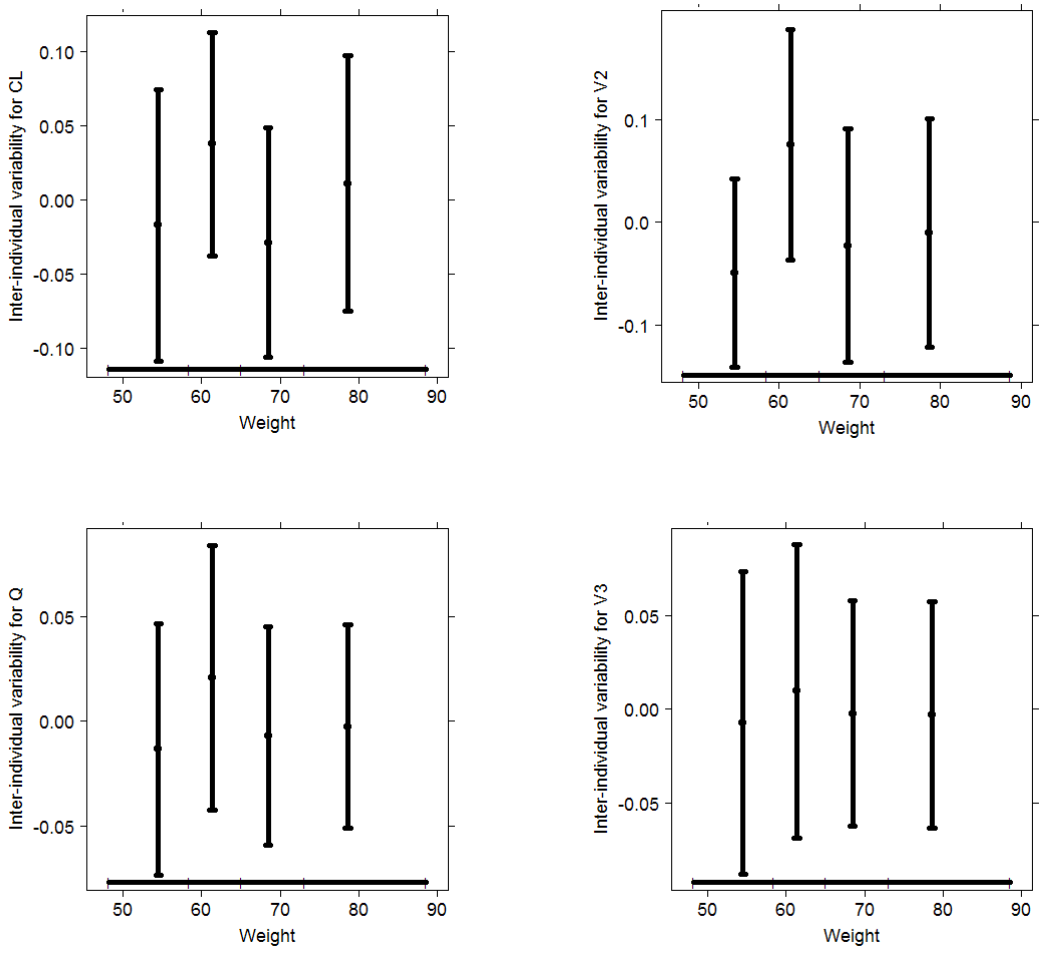
PI was calculated for the overall population grouped by race (black, white, other) and further divided based on categorical body weight cut points (i) <60, 60-80, and >80 kg; and ii) <70, 70-90, and >90 kg). This exploratory analysis was performed to explore the impact of body weight on PI.

Results

Population PK Analysis

Based on goodness of fit plots, OFV decrease, and impact on IIV plots, the model structure identified by the sponsor appended with separate body weight power law covariates on CL, Q, V_c, and V_p was selected. Model evaluation with body weight on a single parameter or with separate parameters on CL and V_c resulted in modest changes in the OFV (decreases of 0 to -3) and power law parameter estimates of 0.06 to 0.1. However, inclusion of separate covariates on all four parameters resulted in an OFV decrease of 50 (from 33178.892 to 33128.339), power law covariate estimates of 0.70, 0.46, 1.20, and 1.19 for CL, V_c, Q, and V_p, respectively, slight decreases in the estimated IIV for all four parameters, and elimination of the body weight relationship from the IIV plots for all four parameters.

Figure 13: Interindividual Variability Plots for CL, V_c (V2), Q, and V_p (V3) Versus Body Weight for the Reviewer's Final Model



Reference ID: 3265296

A summary of the final NONMEM parameter estimates is provided below. This analysis demonstrates that a significant body weight effect on ethinyl estradiol pharmacokinetic can be identified from the available data, though it would not be identified with a typical stepwise forward covariate selection approach. This does not rule out that a typical forward stepwise selection approach may have been able to identified body weight as a significant covariate if subjects with body weight >90 kg had been included in the analysis.

Table 11 Parameter estimates for the reviewer's analysis evaluating inclusion of body weight in the sponsor's final model

Fixed-Effects Parameters	Estimate	RSE(%)	
KA (Oral Absorption, 1/h)	1.9	3.5	
D_1 (Zero-order Absorption, h)	0.69	3.1	
Typical CL/F (Clearance, L/hr)	50.2	6.0	
Proportional multidose Shift on CL	-0.16	18	
Effect of body weight on clearance	0.70	83	
CL/F= TV CL (1-0.16*Shift CL)*(WT/70)$^{0.70}$			
Typical V_c/F (Central volume, L)	377	6.7	
Proportional multidose Shift on V_c	-0.20	14.8	
Effect of body weight on V_c	0.46	108	
V_c/F= TV V_c (1-0.20*Shift V_c)*(WT/70)$^{0.46}$			
Q/F (Intercompartment Transit, L/h)	66	6.7	
Effect of body weight on Q	1.20	35	
Q/F= TV Q*(WT/70)$^{1.20}$			
V_P (Periph Volume)	537	5.8	
Effect of body weight on V_P	1.19	25.6	
V_P/F= TV V_P *(WT/70)$^{1.19}$			
F1 (Seasonique, Seasonale)	1.17	4.6	
Inter-Individual Variability Parameters (CV%)	**Estimate**	**RSE(%)**	**Shrinkage(%)**
KA	29	13	27
D1	34	7.6	12
CL	27	6.7	1.1
V_c	35	7.5	2.1
Q	19	12.3	6.2
V_P	25	6.5	12
Intra-Individual Variability Parameters (sigma)	**Estimate**	**RSE(%)**	
Additive Error	1.4	27	4.3
Proportional Error	0.16	4.6	4.3

Note: CL, V_c, Q and V_p were body weight normalized (70 kg).

Based on the sponsor's model and their posthoc clearance predictions, the sponsor predicted a 25% difference in AUC between subjects in the 1st body weight quartile (median body weight in the quartile of 54.5 kg) and the 4th body weight quartile (median body weight in the quartile of 78.6 kg). This prediction is slightly lower than the exposure difference predicted by the above model based on a body weight of 54.5 kg compared to 78.6 kg (29% difference in AUC).

Reference ID: 3265296

The relationship can be used to obtain predictions for the difference in exposure expected for a typical subject weighing 60 kg compared to a subject weighing 100 kg (predicted 43% difference in exposure) which is approaching the magnitude difference between two already approved products (LoSeasonique and Seasonique), approaches the difference between the lowest dose and the highest dose in the current regimen (20 mg EE versus 30 mg EE), and exceeds the difference between the two lowest ascending doses of the current regimen (20 mg EE versus 25 mg EE). Given the identified body weight impact on EE exposure, the various doses in the current regimen or that are already approved, and the observed difference in PI for subjects with body weight >90 kg (see below), it questions whether the lowest dose in the current regimen and the already approved LoSeasonique will provide sufficient exposures for subjects with body weight >90 kg. However, the information available from the current submission is insufficient to address this question as no pharmacokinetic data was collected during the Phase III trial.

Race and Body Weight Impact on PI

Distribution of body weight grouped by race is shown below in Table 12. The overall weight distribution between patients with race listed as white (n=1952; median: 67.6 kg) and other (n=492; median: 64.9 kg) was similar. In contrast, subjects with reported race as Black or African American (B/AA) had a median body weight of 77.0 kg. During the course of the review cycle, it was identified that subjects with higher body weight (based on a body weight cut point of 90 kg) had a higher pearl index than subjects with body weight <90 kg (Table 12). Likewise, B/AA patients were also more likely to have a higher pearl index than other patients.

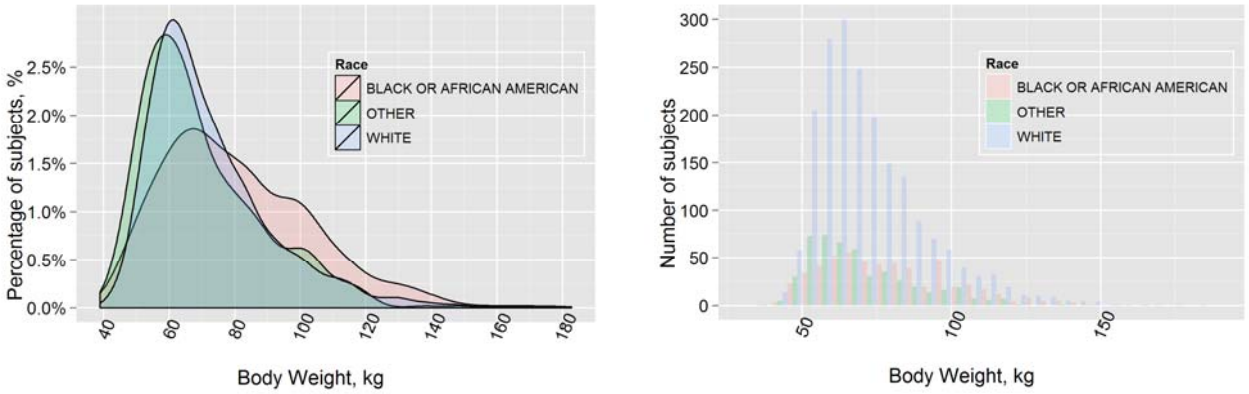
Table 12: Pearl Index from DR-103-301, Grouped By Race or Body Weight Categories for a 28-day cycle equivalent

Body weight	N	# on treatment pregnancies	Number of cycles	Number of BCM cycles	Number of Complete cycles	Pearl Index	95% CI
<70 kg	1607	31	16525	940	15585	2.59	(1.76; 3.67)
>=70-<90 kg	850	21	8644	572	8072	3.38	(2.09; 5.17)
>=90 kg	535	18	5194	336	4858	4.82	(2.86; 7.60)

Race	N	# on treatment pregnancies	Number of cycles	Number of BCM cycles	Number of Complete cycles	Pearl Index	95% CI
Black/African American	548	22	5186	381	4805	5.95	(3.73; 9.00)
Non-Black/African American	2444	48	25177	1467	23710	2.63	(1.94; 3.49)

However, the body weight distribution plots shown below demonstrate that these two demographics may be confounded (i.e., B/AA patients were also more likely to be patients weighing ≥90 kg). Patients with race listed as Asian, Other, Unknown, American Indian or Alaska Native, or Native Hawaiian were grouped as 'Other' in Figure 14 below and comprised 16% of the overall population.

Figure 14: Distribution and count of body weight grouped by race for DR-103-301



The impact of these covariates was explored by looking at estimated pearl index, grouped by race category (Black/African American versus non-Black/African America) and based on categorical body weight groups. First, it should be noted that the confidence intervals for patients with race listed as B/AA are wide due to a small number of subjects/cycles. Second, there are fewer patients with body weight ≥90 kg (18%) in this study, limiting conclusions that can be made with respect to patients with higher body weight.

However, the analyses below demonstrate that both body weight and race (B/AA) may both be contributing factors to an increased PI, and that the increase in PI for B/AA is not entirely explained by the differences in body weight as described within their response to the December 17th 2012 Information Request (SQN 009). For non-B/AA patients, the estimated PI was numerically better for subjects <90 kg compared to patients ≥90 kg (4.10), and the PI increased across the three body weight categories (<70 kg, ≥70-<90 kg, ≥90 kg) (Table 13). A similar trend was observed when the weight categories were altered to <60 kg, ≥60-<80 kg, ≥80 kg, which more closely divided the non-B/AA patients into three groups of approximately similar number. Consistently among non-B/AA patients, a higher PI was observed in the subgroup with the higher body weight.

The overall PI rate was numerically higher among B/AA patients compared to non-B/AA patients across all body weight categories. For B/AA patients with body weight <90 kg, the PI was lower compared to B/AA patients with body weight ≥90 kg (PI [95% CI]: 6.6 [2.7; 13.6]) (Table 13). A less consistent trend was observed for body weight categories of <60 kg, ≥60-<80 kg, ≥80 kg, but the PI for the lowest weight category (<60 kg) remained smaller than that of the other two weight categories. Also, it should be noted that due to the higher body weight among B/AA subjects, this body weight categorization was not as evenly divided among the three categories (compared to categories of <70 kg, ≥70-<90 kg, ≥90 kg). The results shown in Table 12 and Table 13 are also depicted graphics in **Figure 15** to assist in visually comparing the PI across the various weight categories.

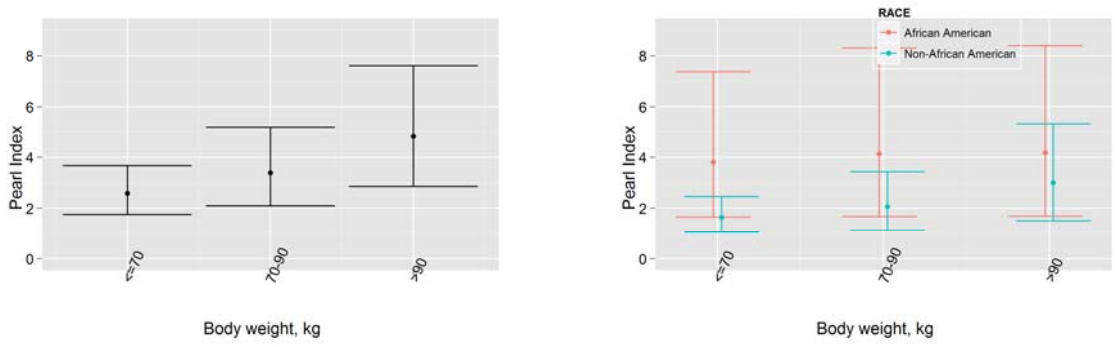
Table 13: Pearl Index from DR-103-301, Grouped By Race Based on Body Weight Categories for a 28-day cycle equivalent

Reference ID: 3265296

Race	Body weight	N	# on treatment pregnancies	Number of cycles	Number of BCM cycles	Number of Complete cycles	Pearl Index	95% CI
Black/African American	<70 kg	210	8	2069	133	1936	5.37	(2.32; 10.56)
	>=70-<90 kg	170	7	1614	116	1498	6.07	(2.44; 12.49)
	>=90 kg	168	7	1503	132	1371	6.64	(2.67; 13.64)
Non-Black/African American	<70 kg	1397	23	14456	807	13649	2.19	(1.39; 3.29)
	>=70-<90 kg	680	14	7030	456	6574	2.77	(1.51; 4.64)
	>=90 kg	367	11	3691	204	3487	4.10	(2.05; 7.33)

Race	Body weight	N	# on treatment pregnancies	Number of cycles	Number of BCM cycles	Number of Complete cycles	Pearl Index	95% CI
Black/African American	<60 kg	103	3	1010	76	934	4.18	(0.86; 12.17)
	>=60-<80 kg	196	9	1828	116	1712	6.83	(3.13; 12.94)
	>=80 kg	249	10	2348	189	2159	6.02	(2.89; 11.05)
Non-Black/African American	<60 kg	730	11	7523	399	7124	2.00	(1.00; 3.59)
	>=60-<80 kg	1077	22	11161	659	10502	2.72	(1.71; 4.12)
	>=80 kg	637	15	6493	409	6084	3.21	(1.79; 5.28)

Figure 15: Pearl Index from DR-103-301, for All Subjects or Grouped by Base into Three Body Weight Categories for a 28-day cycle equivalent



There is a consistent trend of a higher calculated PI for higher body weight categories regardless of race. Likewise, there is a consistently higher calculated PI for B/AA patients regardless of the weight category. While B/AA patients had a higher median body weight at entry compared to other races, this imbalance in body weight does not explain the calculated difference in PI for B/AA patients, and it is likely that both race (B/AA) and higher body weight may be contributing factors to an increased likelihood of contraceptive failure based on the results from this study.

The impact of body weight on PI may be associated with decreased exposure as described above in the population PK analysis. However, the lack of PK sampling in DR-103-301 and the limited number of subjects with body weight >90 kg hinders further evaluation of this hypothesis in the context of this study. Future studies should collect pharmacokinetic data during Phase II and/or III to further assist evaluation of the impact of body weight on exposure and exposure on response. The impact of race on response in the current analysis was not associated solely with body weight, and there may be other study factors to consider (i.e., behavioral, adherence, etc.) when interpreting the role of race on treatment response. Similarly, the role of body weight on response may also be influenced by factors beyond exposure, including study factors such as

Reference ID: 3265296

adherence or differences in the exposure necessary to achieve the desired clinical result (e.g., a higher concentration may be necessary for response in subjects with higher body weight).

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Distribution_weight_Race_for_PI.R	Body weight summary by race and PI calculation for race based on various body weight categories	Reviews\Ongoing PM Reviews\Levorgestrel_NDA204061_JAF\ER Analyses
Run4 mod	Sponsor's final model	Reviews\Ongoing PM Reviews\Levorgestrel_NDA204061_JAF\PPK Analyses
Run6 mod, Run7 mod, Run8 mod, Run9 mod	Include body weight as a power law relationship on model parameters (final model – run8.mod)	Reviews\Ongoing PM Reviews\Levorgestrel_NDA204061_JAF\PPK Analyses

4.4 Filing Memo

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**		

Reference ID: 3265296

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:				
hepatic impairment:				

Reference ID: 3265296

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				

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 demonstrate effectiveness, if the drug is indeed effective?			X	waiver and deferral

Reference ID: 3265296

					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.

Reference ID: 3265296

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 (800081 and 210013) Midrange tablets (800080 and 210012) High-dose tablets (800079 and 210011) Portia tablets (301430 and 302271) Seasonale tablets (800077 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)

Reference ID: 3265296

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)

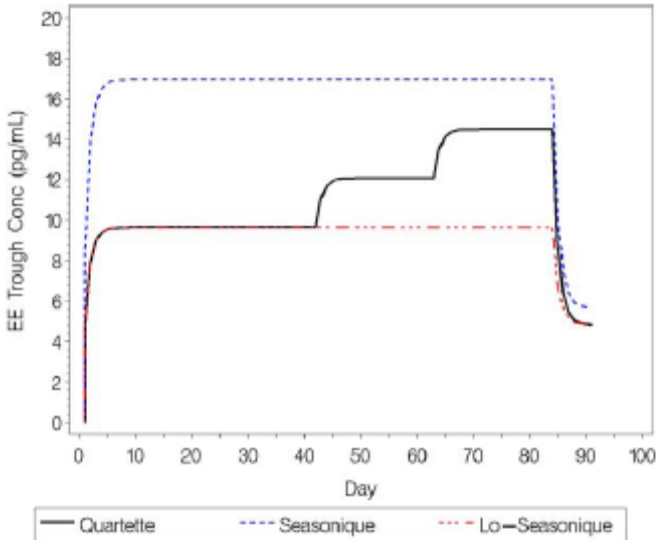
Reviewer's Comments:

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**.

Reference ID: 3265296

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

Reference ID: 3265296

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
02/22/2013

JEFFRY FLORIAN
02/22/2013

YANING WANG
02/22/2013

MYONG JIN KIM
02/22/2013