CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204061
Supplement #:	
Drug Name:	Quartette (levonorgestrel/ethinyl estradiol 0.15mg/0.020 mg, 0.15mg/0.030mg and 0.01mg ethinyl estrodiol) tablets
Indication(s):	Pregnancy Prevention
Applicant:	TEVA PHARMACEUTICAL PRODUCTS R&D, INC.
Date(s):	Submission Date: 05/31/2012
	PDUFA Date: 03/31/2013
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Jia Guo, Ph.D.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Products, HFD-580
Clinical Team:	Vaishali Popat, M.D. Clinical Reviewer
	Lisa Soule, M.D. Clinical Team Leader
Project Manager:	Pamela K. Lucarelli

Keywords:
Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

The study results support the efficacy of Quartette, a 91-day combination oral contraceptive, in preventing pregnancy as demonstrated by the Pearl Index of 3.19 (95% Confidence Interval: 2.49 to 4.03).

The submission contains data from a single multicenter, open-label, one arm study to demonstrate the safety and efficacy of a 91-day combination oral contraceptive consisting of ascending doses of EE in the following regimen

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

The Clinical Division determined that three additional pregnancies should be counted in the analysis. Therefore, FDA analysis included these additional pregnancies in the evaluation of the Pearl Index and life table analyses.

In the study DR-103-301, the Pearl Index based on all subjects aged 18 to 35 years in the intent-to-treat population was 3.19 (95% C.I.: 2.49 to 4.03). Pearl Index of 28-day cycle equivalents appeared to vary substantially by race: 2.72 (95% CI: 1.95 to 3.71) for Whites, 5.95 (95% CI: 3.73 to 9.00) for Blacks, and 2.25 (95% CI: 0.97 to 4.43) for others. Result for subjects with body weight < 90 kg was 2.86 (95% C.I.: 2.13 to 3.75) and for subjects with body weight ≥ 90 kg was 4.82 (95% C.I.: 2.86 to 7.60), respectively. The effectiveness of Quartette appeared to be attenuated in Blacks and in women with body weight ≥ 90kg.

2 INTRODUCTION

2.1 Overview

The Applicant, TEVA seeks approval of Quartette (levonorgestrel (LNG)/ethinyl estradiol(EE) 0.15mg/0.020 mg, 0.15mg/0.030mg and 0.01mg EE) tablets for pregnancy prevention.

Quartette is a 91-day combination oral contraceptive consisting of ascending doses of EE in the following regimen:

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

According to the Applicant, "it was developed to systematically increase the estrogen dose at strategic points in the extended cycle when breakthrough bleeding is likely to occur, in order to reduce the incidence of overall breakthrough bleeding, while lowering the total estrogen exposure per 91-day extended cycle."

The Applicant has submitted one multicenter, open-label, single arm phase 3 study to support the efficacy and safety of Quartette in sexually active women aged 18 to 40 years who desire pregnancy prevention. Table 1 shows a brief summary of the study.

Table 1: Brief Summary of Clinical Study for Quartette

Study Number	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
DR-103-301	*Phase 3 Open-label Multicenter Single arm*	*1 year*	*3 weeks*	*Enrolled:3701 Treated:3597*	▪ *18-40 years old sexually active females at risk for pregnancy*

Source: Reviewer's summary based on study report.

2.2 Data Sources

The study reports, data, statistical programs and additional information for this submission were submitted electronically. The SAS data sets for the study were complete and documented. These items are located in the Electronic Document Room at \\Cdsesub1\evsprod\NDA204061 under submission dates 05/31/2012 and 09/30/2012.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Both tabulation and analysis data sets including the definition files were submitted. Two issues that could have potentially impacted the efficacy evaluation were identified as follows:

(1) The Applicant's definition of "on-drug" pregnancies did not follow the Division's standard convention, i.e. "on drug" pregnancies as those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than seven days after the last tablet taken (whether the combination or EE-alone tablet).

(2) One study Site LA0012 was terminated prematurely during the study, yet there was no discussion of the impact of this site on the safety and efficacy data.

These two issues were communicated to the Applicant on the filing communication letter. The Applicant accepted the Division's definition for "on-drug" pregnancy in (1) and submitted the updated data sets and analysis results using this convention. Efficacy analysis results of the overall study inclusive and exclusive of data from this site were submitted by the Applicant to address (2).

3.2 Evaluation of Efficacy

The study under the current review is DR-103-301 and the data from the terminated site LA0012 is not part of this review.

3.2.1 Study Design and Endpoints

Study DR-103-301 was a multi-center, open-label, single treatment phase 3 trial which consisted of a screening period of approximately 4 weeks, an open-label treatment period of 1 year (four 91-day cycles), and a post-treatment period of approximately 3 weeks. The study enrolled sexually active females who were at risk for pregnancy and 18 through 40 years of age at the time of the screening visit. During the treatment period, clinical visits were scheduled at Weeks 4, 8, 13, 19, 26, 39, 52 (or final visit).

All subjects who met entry criteria and agreed to participate were enrolled in the study and received the following 91-day cycle DR-103 regimen:

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

All subjects were instructed to take one tablet daily at approximately the same time each day. All subjects were "Sunday starters" and remained Sunday starters throughout the duration of the study. During the study, all subjects completed a daily diary to record study medication use, occurrence and severity of bleeding and/or spotting, the use of condoms or other non-hormonal BCMs weekly, as well as use of all concomitant medications.

The incidence of pregnancy was the primary measure in this study. The primary efficacy was evaluated based on Pearl Index (PI) in the group of women who were 35 years of age or less including all at-risk cycles during which no other method of birth control had been used. The Pearl Index based on all risk

cycles where no other method of birth control was used was calculated as follows for both the 91-day cycle and the 28-day cycle-equivalent:

a. (100) x (total number of 'on-drug' pregnancies) x (4)/(total number of 91-day cycles)
b. (100) x (total number of 'on-drug' pregnancies) x (13)/(total number of 28-day cycles)

The "on drug" pregnancies are defined as those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than seven days after the last tablet taken (whether the combination or EE-alone tablet).

3.2.2 Statistical Methodologies

Pearl Index was calculated as defined above and the 95% confidence interval was provided using the binomial method. No formal Pearl Index threshold to meet or statistical hypothesis tests were planned. In the Pearl Index calculation, the cycle in which a subject became pregnant would be considered as a completed cycle regardless of whether the subject had taken all the pills required to complete that cycle. Also, the time after conception date was not counted in the exposure duration for cycle calculation.

Cumulative pregnancy rates at 52 weeks, at each 13-week (91-day) interval, and at equivalent 28-day cycles were estimated using the life table method. The life table analysis was performed using all cycles. A subject who became pregnant while on treatment was considered as having an event on the date of conception. If the conception date was unknown, the date of the last dose was used to estimate the event date. Estimates of pregnancy rates and the corresponding 95% CI were reported by treatment interval.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition of study subjects for DR-103-301 is summarized by in Table 2. A total of 3701 subjects were enrolled, 3597 (97.2%) subjects took at least one dose of IP (Safety population). Of the 3597 subjects who started treatment, a total of 2144 treated subjects (59.6%) completed the study. The primary reasons for study discontinuation were "adverse event" and "lost to follow-up".

Table 2: Summary of Subjects Disposition

	Overall	Excluding Site LA0012
Number Enrolled	3701	3667
Number Treated	3597 (100%)	3565 (100%)
PITT population n (%*)	3019 (83.9%)	2992
Discontinued n (%*)	1453 (40.4%)	1421(40.9%)
Primary Reason for Discontinuation n (%*):		
Adverse Event	466 (13.0%)	457(12.8%)
-bleeding and/or spotting related	167 (4.6%)	162 (4.5%)
Lost to Follow-up	480 (13.3%)	472(13.2%)
Non-compliant	137 (3.8%)	137(3.8%)
Investigator Discretion	5 (0.1%)	5(0.1%)
Pregnancy	68 (1.9%)	68(1.9%)
Protocol Violation	16 (0.4%)	16(0.5%)
TEVA Requested Subject's Withdrawal	35 (1.0%)	21(0.6%)
Subject Request to be Withdrawn	217 (6.0%)	216(6.1%)
Other	29 (0.8%)	29(0.8%)

Source: Table 3 in the study report and reviewer's calculation.
Denominator for % calculation is the number of subjects treated.

The primary population for evaluating the efficacy of Quartette was the pregnancy intent-to-treat population (PITT), which included subjects who had completed at least one 28-day cycle-equivalent of study medication and were between 18 and 35 years of age. The PITT population had a total of 3019 subjects and 2992 subjects excluding site LA-0012. The mean age of the treated subjects was 25.9 years old and the majority of subjects were Caucasian (65.5%) in the PITT population.

3.2.4 Results and Conclusions

Table 3 presents the Pearl Index results using complete 28-day cycle-equivalents for Quartette in the PITT population. The Applicant reported 67 on-drug pregnancies and a Pearl Index of 3.05 (95% CI: 2.37-3.88). After close review of the submitted pregnancy data, the clinical/statistical team identified three additional "on-drug" pregnancies. For two of these three pregnancies, the clinical reviewer found that the conception date should be one day earlier than the dates reported by the Applicant and the conception date was in the 7-day window after last dose. The third pregnancy occurred during the study, but the subject was lost to follow-up. By The Division's convention, such pregnancy should be considered as "on-drug". The Pearl Index calculated by the reviewer is 3.19 (95% CI: 2.49-4.03).

Reviewer's comments:
The findings of additional 3 pregnancies were communicated to the Applicant through email on Nov 21.2012. The Applicant's response on Dec 21, 2012 confirmed that they accepted the Division's request to consider these 3 pregnancies as "on-drug".

Table 3: Summary of Pearl Index analyses for complete 28-day cycle-equivalent – PITT population

	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	2992	70	30363	1848	28515	3.19	(2.49, 4.03)

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

Table 4 presents the Pearl Index results for 91-day cycles for Quartette in the PITT population. The sponsor-reported Pearl Index is 3.37 (95% CI: 2.61-4.27) and the reviewer-reported Pearl Index is 3.52 (95% CI: 2.75-4.44).

Table 4: Summary of Pearl Index analyses for complete 91-day cycles – PITT population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
Applicant	2747	67	9164	1207	7957	3.37	(2.61, 4.27)
Reviewer	2747	70	9164	1207	7957	3.52	(2.75, 4.44)

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

By excluding site LA-0012, the Applicant's estimated life table pregnancy rate in all treated subjects 18-35 years of age using 67 pregnancies and all 91-day cycles is 2.72 % (95% C.I. 2.13% to 3.46%, source: Table 8.6, response-to-fda-set-2.pdf Appendix B), and 2.69 % (95% C.I. 2.11% to 3.42%, source: Table 8.9, response-to-fda-set-2.pdf Appendix B) using all 28-day equivalent cycles.

The Reviewer's estimated life table pregnancy rate in all treated subjects 18-35 years of age using 70 pregnancies and all 91-day cycles is 2.85% (95% C.I. 2.25% to 3.61%), and 2.82% (95% C.I. from 2.22% to 3.57%) using all 28-day equivalent cycles.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The study was conducted in US and enrolled female subjects only; therefore, analyses by subgroups defined by gender and region were not performed. Pearl Index is calculated by the reviewer for the subgroups defined by race, as White, Black and other.

As shown in Table 5, the Pearl Index of 28-day cycle equivalents appeared to vary substantially by race: 2.72 for Whites, 5.95 for Blacks, 2.25 for others. Similar pattern is observed in Table 6 for Pearl Index of 91-day cycles as well.

Table 5: Pearl Index analyses for complete 28-day cycle-equivalents by race subgroups – PITT population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
White	1952	40	20228	1144	19084	2.72	(1.95, 3.71)
Black or African American	548	22	5186	381	4805	5.95	(3.73, 9.00)
Other	492	8	4949	323	4626	2.25	(0.97, 4.43)

Site LA0012 is excluded.
Source: Reviewer's analysis.

Table 6: Pearl Index analyses for complete 91-day cycles by race subgroups – PITT population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
White	1796	40	6112	759	5353	2.99	(2.14, 4.06)
Black or African American	498	22	1562	239	1323	6.65	(4.17, 10.03)
Other	453	8	1490	209	1281	2.50	(1.08, 4.91)

Site LA0012 is excluded.
Source: Reviewer's analysis.

4.2 Other Special/Subgroup Populations

In study DR-103-301, Pearl Index is also calculated for subgroups of subjects based on baseline body weight (<90kg, >=90kg).

The mean and median of body weight at the start of the study for PITT cohort were 73.5 kg and 68.6 kg, respectively, and about 18% of the subjects recruited in this study had body weight greater or equal than 90 kg. As shown in Table 7, Pearl Index of 28-day cycle equivalents for subjects <90 kg in PITT population is 2.86 (95% C.I.: 2.13 to 3.75) and for body weight ≥90 kg is 4.82 (95% C.I.: 2.86 to 7.60), respectively. Similar pattern is observed in Table 8 for Pearl Index of 91-day cycles as well.

Table 7: Pearl Index analyses for complete 28-day cycle-equivalents by body weight subgroups – PITT population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
<90kg	2457	52	25169	1512	23657	2.86	(2.13, 3.75)
>=90kg	535	18	5194	336	4858	4.82	(2.86, 7.60)

Site LA0012 is excluded.
Source: Reviewer's analysis

Table 8: Pearl Index analyses for complete 91-day cycles by body weight subgroups – PITT population

	N	Number of On-Treatment Pregnancies	Number of Cycles	Number of BCM Cycles	Number of Complete Cycles	Pearl Index	95% CI
<90kg	2258	52	7592	976	6616	3.14	(2.35, 4.12)
>=90kg	489	18	1572	231	1341	5.37	(3.19, 8.45)

Site LA0012 is excluded.
Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

From a statistical perspective, the study results support the efficacy of Quartette, an oral regimen of levonorgestrel (LNG)/ethinyl estradiol(EE) 0.15mg/0.020 mg, 0.15mg/0.030mg and 0.01mg EE), in the prevention of pregnancy. The effectiveness of Quartette appeared to be attenuated in Blacks, and in women with a body weight ≥ 90 kg.

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/s/

JIA GUO
02/22/2013

MAHBOOB SOBHAN
02/22/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 20-4061 **Applicant:** TEVA BRANDED PHARMACEUTICAL PRODUCTS R AND D INC **Stamp Date:** May 31, 2012

Drug Name: Quartette (levonorgestrel and ethinyl estradiol) **NDA/BLA Type: New**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			Only one phase III efficacy study was conducted. ISE is not applicable.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	√			Subjects are female only. Subgroup analysis was done by BMI.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials	√			

File name: 5_Statistics Filing Checklist for a New NDA_202276

in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			√	

The review issue noticed:

1. In the statistical analysis plan and Table 25, listing of pregnancies that occurred in treated subjects, in study 103-301 study report, the statistical reviewer noticed that the sponsor defined pregnancy as "on-drug" if IP Start date < Conception date < last dose date of Combination IP + 7.

   The Division defined the "on-drug" pregnancies as those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than seven days after the last tablet taken (**whether the combination or EE-alone tablet**).

Requests to the Applicant on 74-day letter:

For study 103-301,

1. Submit the statistical programs that generated analysis datasets, d_adpreg.xpt, d_adeff.xpt, d_adsl.xpt and d_adcyc.xpt from tabulation data.
2. Submit the statistical programs that calculate Pearl index and conduct life table analyses.
3. In d_adpreg.xpt, data on conception date is available, but the reviewer can't find the conception date data in the tabulation dataset FA.xpt. Clarify the data source of conception date. If it was derived, provide the derivation method; if it was collected, submit the raw data.
4. Subject 10029041 from site FL-0029 is in dataset d_adpreg.xpt, but not in tabulation dataset FA.xpt. Clarify this discrepancy.
5. The sponsor defined pregnancy as "on-drug" if IP Start date < Conception date < last dose date of Combination IP + 7. Clarify what the "last dose date of **Combination IP**" means exactly.

Jia Guo, Ph.D. 07/30/2012
Reviewing Statistician Date

Mahboob Sobhan, Ph.D. 07/30/ 2012
Supervisor/Team Leader Date

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/s/

JIA GUO
07/30/2012

MAHBOOB SOBHAN
07/30/2012