CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-573 / N000
Drug Name:	WC3026 (Norethindrone 0.8 mg/Ethinyl estradiol 0.025 mg tablets)
Indication(s):	Prevention of Pregnancy
Applicant:	Warner Chilcott Company, Inc.
Date(s):	Submission Date: 11/26/2009
	PDUFA Date: 9/26/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
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Keywords: Clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study results support the efficacy of WC3026, a 28-day low dose combination oral contraceptive (COC), in preventing pregnancy as demonstrated by the Pearl Index of 2.01 (95% Confidence Interval: 1.21 to 3.14).

1.2 Overview of Clinical Studies

The submission contains data from a single multicenter, open-label, one arm study to demonstrate the safety and efficacy of a low-dose, combination oral contraceptive regimen WC3026 taken for thirteen-28 day cycles in women desiring pregnancy prevention. This COC consists of a new combination regimen of combination of norethindrone 0.8 mg/ethinyl estradiol 0.025 mg (NE 0.8 mg/EE 0.025 mg) for 24 days followed by 4 days of a placebo tablet.

1.3 Statistical Issues and Findings

The Clinical Division determined that one additional pregnancy should be counted in the analysis. Therefore, in this review, our analysis included this additional pregnancy in the evaluation of efficacy using the Pearl Index and Life Table analyses.

In the pivotal study PR-00207, the Pearl Index based on all subjects aged 18 to 35 years in the intent-to-treat (PITT) population was 2.01 (95% C.I.: 1.21 to 3.14). Result for subjects with body mass index (BMI) less than or equal to 30 is 1.86 (95% C.I: 1.04 to 3.06) and for BMI between 30 and 35 is 2.89 (95% C.I.: 0.79 to 7.38), respectively. The effectiveness of WC3026 appeared to be attenuated in women with a BMI > 30 kg/m^2.

2. INTRODUCTION

2.1 Overview

The Applicant, Warner Chilcott Company, Inc., is seeking approval of WC3026, a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone (NE) and ethinyl estradiol (EE), in the prevention of pregnancy. The dosing regimen consists of norethindrone 0.8 mg/ethinyl estradiol 0.025 mg (NE 0.8 mg/EE 0.025 mg) oral tablets administered for 24 days of 28-day cycle, followed by 4 days of a placebo tablet. The Applicant expected this regimen to be safe and effective and lead to a reduction in total and unscheduled monthly bleeding.

The Applicant has submitted one multicenter, open-label, single arm study with thirteen-28 day cycles of use to support the safety and efficacy of WC3026 oral contraceptive in sexually active women aged 18 to 45 years who desire pregnancy prevention. Approximately 1600 women of childbearing potential were treated with up to thirteen 28-day cycles of drug regimen in which NE 0.8 mg/EE 0.025 mg was administrated for 24 consecutive days. Table 1 shows a brief summary of the study.

Table 1: Brief Summary of Clinical Study for WC3026

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Sample Size (MITT[1])	Duration of Treatment	Design[2]
PR-00207 (70 / U.S.) 06-21-07 to 01-23-09	Heterosexually active females who were at risk of pregnancy with 18-45 years of age and BMI ≤ 35	WC3026	1677 (1570)	thirteen-28 Day cycles of WC3026	OL, MC, U

[1] MITT = subset of all treated population who were evaluated for at least once after beginning the study medication
[2] OL = Open Label, MC = Multicenter, U = Uncontrolled

2.2 Data Sources

The study reports and additional information for this submission are available in electronic format. The SAS data sets for the study were complete and well documented. These items are located in the Electronic Document Room at \\Cdsesub1\evsprod\NDA022573\0000 under submission date 12/1/2009.

2.3 Indication

WC3026 is indicated for the prevention of pregnancy.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study PR-00207 was a multi-center, open label, single arm study of a 28-day oral contraceptive tablet containing NE 0.8 mg and EE 0.025 mg oral tablets administered for 24 days followed by 4 days of a placebo tablet. The objective of the study was to demonstrate the safety and efficacy of WC3026 in the prevention of pregnancy.

Heterosexually active women aged 18 to 45 years and at risk of becoming pregnant were enrolled into the study and assigned to take WC3026 daily for thirteen-28 day cycles of treatment. All pregnancies occurring during the study and within 30 days after the end of treatment were assessed to determine their relationship to the use of the products in this study. Pregnancies found to have an estimated date of conception more than 7 days after the end of drug intake were not counted. All other pregnancies were considered to have occurred during treatment.

Each subject kept a daily record of her bleeding occurrences in a diary. Bleeding and spotting frequencies and patterns were evaluated.

The Modified intent-to-treat cohort (MITT) consists of all treated patients who were evaluated for pregnancy, either positive or negative, at least once after beginning of the study medication. The Completed population was defined as the subset of MITT subjects who completed at least 360 days of treatment based on the diary reports. The pregnancy intent-to-treat cohort (PITT) consisted of women in the MITT cohort between the ages of 18 and 35 at the initiation of study drug. There was no Per Protocol population defined in this study: subjects were included in the analysis regardless of their compliance with planned study procedures.

The incidence of pregnancy was the primary measure in this study. The primary efficacy was evaluated based on Pearl Index in the group of women 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 for all subjects, regardless of age, based on all risk cycles where no other method of birth control was used was presented. The Pearl Index was calculated as follows:

Pearl Index = 1300 × (number of pregnancies) / (number of woman-cycles of treatment)

The 95% confidence limits for the Pearl Index were computed as 1300 times the exact binomial confidence limits with the number of pregnancies and the number of woman-cycles of treatment. The life-table method was performed using log rank tests.

3.1.2 Results

Patient Disposition: Table 2 summarizes the number of randomized subjects and the disposition of all treated subjects. The primary reason for study discontinuation in study PR-00207 was "lost to follow-up" (16.2%), "Withdrew Consent" (8.9%) and "Adverse Events" (8.5%). In the MITT population, the mean age was 28.8 years with an age range of 18 to 46 years, 48% of the patients were new start and the majority (72%) of subjects was Caucasian.

Table 2: Randomization and Disposition of All Treated Patients for Study PR-00207

	n (%)
Subjects who received therapy	1677
MITT population, [a]	1570 (93.6)
Evaluable for IB for all Cycles[b] 2-13	1425 (85.0)
Completed subjects[c]	746 (44.5)
Discontinued Subjects	
Lost to Follow-up	271 (16.2)
Adverse Events	143 (8.5)
Withdrew Consent	149 (8.9)
Other reasons	75 (4.5)
Lack of Efficacy (Pregnancy)	23 (1.4)
Death	0
Protocol Violation	25 (1.5)

MITT = modified intent-to-treat; IB = intracyclic bleeding

a: The MITT population was defined as the subset of the All Treated population who were evaluated for pregnancy, whether positive or negative, at least once after beginning the study medication.

b: A cycle was considered evaluable if at least 14 evaluable diary days were available.

c: The Completed Subjects population was defined as the subset of MITT subjects who completed at least 360 days of treatment based on the diary reports.

(Source: Clinical Study Report RR-03009; Table 4, page 39)

Efficacy Results: Table 3 presents the Pearl Index for WC3026 in MITT and PITT population. For the PITT cohort, the Sponsor included 18 pregnancies with a Pearl Index of 1.90; while our review included one additional pregnancy for a total of 19 pregnancies with a Pearl Index of 2.01 (95 C.I.: 1.21 to 3.14).

Table 3: Pearl Index Calculation of Treatment Failure Rates: Results of Sponsor and FDA Analysis

	Population	Subject Exposed (n)	On-Treatment Pregnancies (n)	Cycles (n)	Pearl Index (95% CI)
Applicant	MITT	1,570	19	15,752	1.57 (0.94, 2.45)
	PITT	1,251	18	12,297	1.90 (1.13, 3.01)
FDA	MITT	1,570	20	15,752	1.65 (1.01, 2.55)
	PITT	**1,251**	**19**	**12,297**	**2.01 (1.21, 3.14)**

Table 4 summarizes the results of life table analysis of cumulative pregnancy rate. For the PITT cohort, the cumulative failure rate after 13 cycles of treatment was 1.90 as reported by the Applicant based on 18 "on drug" pregnancies. The Applicant did not provide a confidence interval. Our analysis showed a rate of 2.00% (95% C.I.: 1.27% - 3.13%) which was based on 19 "on drug" pregnancies.

Table 4: Life Table Analysis of the Cumulative Failure Rates after thirteen-28 Day Cycles of Treatment: Results of Sponsor and FDA analysis.

	Population	On-Treatment Pregnancies (n)	Cumulative Pregnancy Rate (95% CI)
Applicant	MITT	19	1.57%
	PITT	18	1.90%
FDA	MITT	20	1.75% (1.27%, 2.40%)
	PITT	**19**	**2.00% (1.27%, 3.13%)**

Both analyses consistently demonstrated that WC3026 was effective in preventing pregnancy with the upper bound of 95% CI for the point estimate a little over 3.0, a threshold generally considered acceptable for contraceptives.

3.2 Evaluation of Safety

There was no statistical evaluation of safety data necessary for this review. Detailed safety information can be found in the clinical reviewer's review.

4. FINDINGS IN SUBGROUP OF POPULATIONS

4.1 Race

As shown in Table 5, the Pearl Index appeared to vary substantially by race: 1.90 for Caucasians, 3.36 for Blacks, 1.92 for Hispanics and 0 for others. However, no conclusion can be drawn due to the small sample sizes across subgroups of race.

Table 5: Pearl Index Calculation of Treatment Failure Rates for PITT Cohort by Race

Population	Subject Exposed (n)	On-Treatment Pregnancies (n)	Cycles (n)	Pearl Index (95% CI)
Caucasian	899	13	8,878	1.90 (1.01, 3.25)
Black	161	4	1,546	3.36 (0.92, 8.59)
Hispanic	141	2	1,356	1.92 (0.23, 6.91)
Other	50	0	517	0.00 (0.00, 0.00)
Total	1,251	4	1,800	1.90 (1.13..3.01)

(Source: Reviewer's results)

4.2 BMI

The mean and median of BMI at the start of the study for PITT cohort are 24.0 kg/m^2 and 24.8 kg/m^2, respectively, and about 16% of the subjects recruited in this study had BMI greater than 30. Only one patient had BMI greater than 35 due to protocol violation. As shown in Table 6, Result for subjects in PITT with BMI less than or equal to 30 is 1.86 (95% C.I.: 1.04 to 3.06) and for BMI between 30 and 35 is 2.89 (95% C.I.: 0.79 to 7.38), respectively.

Table 6: Pearl Index Calculation of Treatment Failure Rates by BMI

Population	BMI	Subject Exposed (n)	On-Treatment Pregnancies (n)	Cycles (n)	Pearl Index (95% CI)
PITT	BMI ≤ 30	1,060	15	10,497	1.86 (1.04, 3.06)
	BMI > 30	191	4	1,800	2.89 (0.79, 7.38)
MITT	BMI ≤ 30	1,317	16	13,341	1.55 (0.89, 2.53)
	BMI > 30	253	4	2,411	2.16 (0.58, 5.52)

(Source: Reviewer's results)

5. CONCLUSIONS

From a statistical perspective, the study results support the efficacy of WC3026, a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE), in the prevention of pregnancy. The effectiveness of WC3026 appeared to be attenuated in women with a BMI > 30 kg/m^2.

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/s/

KATE L DWYER
09/17/2010

MAHBOOB SOBHAN
09/17/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA: 22-573 **Applicant:** Warner Chilcott Company, Inc. **Stamp Date:** 11/26/2009

Drug Name: (b) (4) (norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets) **45 day Meeting Date:** 1/07/2010

Indication: Prevention of Pregnancy

Medical Officer: Gerald Willett, M.D. **Project Manager:** Pamela Lucarelli

A: Summary

The sponsor submitted one pivotal Phase III efficacy study in support of WC3016 for pregnancy prevention. Brief summary of the study is shown below.

Brief Summary of Pivotal Phase III Clinical Study for WC3026

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Sample Size (MITT[1])	Duration of Treatment	Design[2]
PR-00207 (70 / U.S.) 06-21-07 to 01-23-09	Heterosexually active females who were at risk of pregnancy with 18-45 years of age and BMI ≤ 35	WC3026	1677 (1570)	thirteen-28 Day cycles of WC3026	OL, MC, U

[1] MITT = subset of all treated population who were evaluated for at least once after beginning the study medication
[2] OL = Open Label, MC = Multicenter, U = Uncontrolled

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.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

B: Conclusion

After preliminary review of the submission of the following checklist items, this submission is fileable from statistical point of view.

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.	X			
Endpoints and methods of analysis are specified in the	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

Kate Dwyer, Ph. D. 1/07/10

Reviewing Statistician Date

Mahboob Sobhan, Ph. D. 1/07/10

Supervisor/Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22573	ORIG-1	WARNER CHILCOTT INC	(b) (4)(norethindrone and ethinyl estradiol tablets, chewable and ferrous fumarate tablets)

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/s/

KATE L DWYER
01/07/2010

MAHBOOB SOBHAN
01/08/2010