

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022501Orig1s000

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: 22-501 / Resubmission

Drug Name: LO LOESTRIN FE (Norethindrone acetate and Ethinyl Estradiol tablets, and Ferrous Fumarate tablets)

Indication(s): Prevention of Pregnancy

Applicant: Warner Chilcott Company, Inc.

Date(s): Submission Date: 4/21/2010
PDUFA Due Date: 10/21/2010

Review Priority: Priority

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Kate Dwyer, Ph.D.

Concurring Reviewers: Mahboob Sobhan, Ph.D.

Medical Division: Division of Reproductive and Urologic Drug Products

Clinical Team: Ronald Orleans, M.D., Medical Reviewer
Lisa Soule, M.D., Team Leader

Project Manager: Karl Stiller

Keywords: Labeling review

BACKGROUND

The Applicant has resubmitted this supplement in response to the Complete Response Letter issued by the Agency on January 26, 2010 regarding several manufacturing deficiencies. This is a labeling review for LO LOESTRIN FE, an oral contraceptive, and no additional clinical trial data was included in this submission. The proposed indication is for the prevention of pregnancy in women [REDACTED] ^{(b) (4)}.

CONCLUSION

The efficacy (using Pearl Index) result in the label was evaluated and verified by this reviewer in the original statistical review of this NDA. Since no additional efficacy data was included in this resubmission, this reviewer agrees with the final version of the label.

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/s/

KATE L DWYER

10/18/2010

re-check in as general review.

MAHBOOB SOBHAN

10/18/2010



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BACKGROUND

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CONCLUSION

The efficacy (using Pearl Index) result of the labeling based on 28 on-drug pregnancies that had occurred over 12,482 completed cycles was calculated by this reviewer in the original statistical review of this NDA. Since no additional efficacy data was submitted, no statistical review was necessary for this labeling change.

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/s/

KATE L DWYER
10/15/2010

MAHBOOB SOBHAN
10/15/2010



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: 22-501 / N000

Drug Name: (b) (4) [pending] (Norethindrone acetate and Ethinyl Estradiol tablets, and Ferrous Fumarate tablets)

Indication(s): Prevention of Pregnancy

Applicant: Warner Chilcott Company, Inc.

Date(s): Submission Date: 3/26/2009
PDUFA Date: 1/26/2010

Review Priority: Standard

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Kate Dwyer, Ph.D.

Concurring Reviewers: Mahboob Sobhan, Ph.D.

Medical Division: Division of Reproductive and Urologic Drug Products, HFD-580

Clinical Team: Ronald Orleans, M.D., Medical Reviewer
Lisa Soule, M.D., Team Leader

Project Manager: Karl Stiller

Keywords: Clinical studies, NDA review

Table of Contents

1. EXECUTIVE SUMMARY	4
1.1 CONCLUSIONS AND RECOMMENDATIONS	4
1.2 OVERVIEW OF CLINICAL STUDIES	4
1.3 STATISTICAL ISSUES AND FINDINGS	4
2. INTRODUCTION	5
2.1 OVERVIEW.....	5
2.2 DATA SOURCES	5
2.3 INDICATION	5
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY.....	5
3.1.1 <i>Study Design</i>	5
3.1.2 <i>Reviewer’s Comment on Study Design</i>	6
3.1.3 <i>Results</i>	7
3.2 EVALUATION OF SAFETY	8
4. FINDINGS IN SUBGROUP OF POPULATIONS	8
5. CONCLUSIONS.....	8

LIST OF TABLES

Table 1: Brief Summary of Clinical Study for WC3016	5
Table 2: Randomization and Disposition of All Treated Patients for Study PR-05806.....	7
Table 3: Pearl Index Calculation of Treatment Failure Rates: Results of Sponsor and FDA Analysis	7
Table 4: Life Table Analysis of the Cumulative Failure Rates after thirteen-28 Day Cycles of Treatment: Results of Sponsor and FDA analysis.....	8
Table 5: Pearl Index Calculation of Treatment Failure Rates for PITT Cohort by race	8

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study results support the efficacy of WC3016, a 28-day low dose combination oral contraceptive (COC), in preventing pregnancy as demonstrated by Pearl Index of 2.92 (95% Confidence Interval: 1.94% to 4.21%). In this study, the Pearl Index appeared to vary substantially by race. However, no conclusion can be drawn due to the small sample sizes in subgroups of race.

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 WC3016 taken for thirteen-28 day cycles in women desiring pregnancy prevention. This COC consists of a regimen of 1 mg norethindrone acetate (NETA) / 10 mcg ethinyl estradiol (EE) oral tablets administered for 24 days of a 28-day cycle, followed by EE 10 mcg for 2 days, followed by an inactive tablet containing ferrous fumarate for 2 days.

1.3 Statistical Issues and Findings

There are two statistical issues identified with this submission: the Applicant's definition of pregnancy intent-to-treat cohort (PITT) population and "on-drug pregnancies" in study PR-05806. The Applicant defined the PITT population as group of women 35 years of age or less based on all at risk cycles where no other method of birth control was used, and censored on their 36th birthday. The division did not agree that subjects should be censored from the PITT population if they were 35 years of age at enrollment but conceived after their 36th birthday.

The Applicant defined an "on-drug pregnancy" as a pregnancy occurring 14 or more days after the first date of study medication and up to and including 14 days after the last day of study medication. The division believes that an "on-drug pregnancy" should be defined as a conception occurring from Day 1 (the initiation of taking study drug) to 7 days after the final tablet was taken. The Agency conveyed this information to the Applicant who subsequently revised their study report in the July 22, 2009 submission. However, one additional pregnancy was identified by the Division after the revision thus making a total of 28 "on drug pregnancies." Therefore, in this review the additional pregnancy was included in the calculation of Pearl Index and Life Table analyses.

The efficacy evaluation was based on the calculation of pregnancy rates using Pearl Index in women aged 18 to 35 years excluding cycles in which they used other birth control methods. In the pivotal study PR-05806, the Pearl Index for WC3016 oral contraceptive for all subjects in the PITT population was 2.92 (95% Confidence Interval: 1.94% to 4.21%). The Pearl Index appeared to vary substantially by race: 2.07 for Caucasians, 2.96 for Blacks, 8.13 for Hispanics and 5.51 for others.

2. INTRODUCTION

2.1 Overview

The Applicant, Warner Chilcott Company, Inc., is seeking approval of a new drug application for (b) (4) is a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). The dosing regimen consists of norethindrone acetate 1 mg/ethinyl estradiol 10 mcg (NA 1/EE 10) oral tablets administered for 24 days followed by 2 days of ethinyl estradiol 10 mcg (EE 10) and 2 days of a placebo tablet. This regimen is referred to as WC3016.

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 WC3016 oral contraceptive in sexually active women aged 18 to 45 years who desire pregnancy prevention. Table 1 shows a brief summary of the study.

Table 1: Brief Summary of Clinical Study for WC3016

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Sample Size (MITT ¹)	Duration of Treatment	Design ²
PR-05806 (68 / U.S.) 11-01-06 to 08-27-08	Heterosexually active females who were at risk of pregnancy with 18-45 years of age and BMI ≤ 35	WC3016	1660 (1582)	thirteen-28 Day cycles of WC3016	OL, MC, U

¹ all treated patients who were evaluated for pregnancy 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 paper format. The SAS data sets for the study were complete and well documented. These items are located in the Electronic Document Room at \\Fds\wa150\none\ctd\N22501\N_000 under submission date 3/26/2009.

2.3 Indication

(b) (4) is indicated for the prevention of pregnancy.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study PR-05806 was a multi-center, open label, single arm study of a 28-day oral contraceptive tablet containing NA 1 mg and EE 10 mcg oral tablets administered for 24 days followed by 2 days of EE 10 mcg and 2 days of a placebo tablet. The objective of the study was to demonstrate the safety and efficacy of WC3016 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 WC3016 daily for thirteen-28 day cycles of treatment. After completion of the treatment phase of the study, all subjects were followed to determine if any pregnancy had occurred in the immediate post-treatment period. 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 14 days after the initiation of study medication and up to and including 14 days after the last day of study medication were counted by the Applicant as being “on drug.”

During the study, all patients completed a daily paper diary to record study drug use, incidence of bleeding or spotting, any additional forms of contraception used, and any concomitant medications.

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 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.

Efficacy was evaluated based on Pearl Index in the group of women 35 years of age or less based on all at risk cycles where no other method of birth control was used. A pregnancy was counted in the Applicant’s initial efficacy analysis if the EDC occurred 14 or more days after the first date of study medication and up to and including 14 days after the last day of study medication. The Pearl Index for all subjects, regardless of age, based on all risk cycles where no other method of birth control was used was also presented. The 95% confidence intervals for the Pearl Indices and life table estimates of a subject becoming pregnant were also presented. The Pearl Index was calculated as follows:

$$\text{Pearl Index} = 1300 \times (\text{number of pregnancies}) / (\text{number of woman-cycles of treatment})$$

No formal statistical testing was planned.

3.1.2 Reviewer’s Comment on Study Design

At the protocol stage, we did not agree with the Applicant’s definition of the pregnancy intent-to-treat cohort (PITT) and “on-drug pregnancies” analysis population. The Division notified the Applicant in the 74-Day letter of the following definitions:

The PITT should be defined as women aged 18 to less than 36 years at the time of enrollment in the clinical trial. The PITT cohort should be the principal analysis cohort for pregnancy evaluation. Subjects in this group should not be censored in the pregnancy assessment if their 36th birthday occurred after study enrollment.

“On-drug pregnancies” was defined as all conceptions that occur from Day 1 (the initiation of taking study drug) to 7 days after the final tablet (i.e., the second Fe tablet) in the pill pack is taken. If the pills were stopped prior to completing a 28-day pack, then “on-drug pregnancies” should be defined as all conceptions from Day 1 (the initiation of taking study drug) to 7 days after the final tablet was taken.

Based on the above definitions of the PITT population and “on-drug pregnancies,” we requested the Applicant to resubmit results of the Pearl Indices and life table pregnancy rates.

3.1.3 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-05806 was “lost to follow-up” (13.7%), “Adverse Events” (10.7%) and “Withdrew Consent” (8.9%). Also, the mean age was 28.6 years, 51% of the patients were new start and the majority (75%) of subjects was Caucasian.

Table 2: Randomization and Disposition of All Treated Patients for Study PR-05806

	n (%)
Subjects who received therapy	1660 (100)
MITT population, ^a	1582 (95.3)
Evaluable for IB for all Cycles ^b 2-13	738 (44.5)
Completed subjects ^c	968 (58.3)
Discontinued Subjects	
Lost to Follow-up	227 (13.7)
Adverse Events	177 (10.7)
Withdrew Consent	147 (8.9)
Other reasons	96 (5.8)
Lack of Efficacy (Pregnancy)	25 (1.5)
Death	0
Protocol Violation	20 (1.2)

(Source: Clinical Study Report RR-03108.0; Table 4, page 44)

Pregnancy Rates: The sponsor’s results were from the resubmission received on July 23, 2009 in response to the 74-Day Letter sent to the sponsor. The original submission for PITT was based on 24 pregnancies instead of 27 pregnancies. One additional pregnancy was identified thereafter by the FDA clinical reviewer.

Table 3 presents the Pearl Index results for WC3016 in MITT and PITT population. For the PITT cohort, the Sponsor included 27 pregnancies with a Pearl Index of 2.81; while our review included one additional pregnancy for a total of 28 pregnancies with a Pearl Index of 2.92. Our calculation excluded all cycles (28-day) in which back-up contraception was used, including condom. However, it counted the cycles in which a pregnancy occurred.

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

	Population	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Sponsor	MITT	1,555	27	15,595	2.25	(1.48, 3.27)
	PITT	1,270	27	12,486	2.81	(1.85, 4.09)
Reviewer	MITT	1,555	28	15,591	2.33	(1.55, 3.37)
	PITT	1,270	28	12,482	2.92	(1.94, 4.21)

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 2.71%, as reported by the Applicant based on 27 “on drug” pregnancies. The Applicant did not provide a confidence interval. Our analysis showed a rate of 2.71% (95% C.I.: 1.86% - 3.95%) which was based on 28 “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	Number of On-Treatment Pregnancies	Cumulative Pregnancy Rate	95% Confidence Interval
Sponsor	MITT	27	2.17%	
	PITT	27	2.71%	
Reviewer	MITT	28	2.17%	(1.49%, 3.17%)
	PITT	28	2.71%	(1.86%, 3.95%)

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

We performed additional analysis by the subgroup of race. As shown in Table 5, the Pearl Index appeared to vary substantially by race: 2.07 for Caucasians, 2.96 for Blacks, 8.13 for Hispanics and 5.51 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

Race	N	Number of On-Treatment Pregnancies	Number of Cycles	Pearl Index	95% Confidence Interval
Caucasian	948	15	9,414	2.07	(1.16, 3.41)
Black	139	3	1,316	2.96	(0.61, 8.64)
Hispanic	137	8	1,280	8.13	(3.51, 15.96)
Others	46	2	472	5.51	(0.67, 19.79)
Total	1,270	28	12,482	2.92	(1.94, 4.21)

(Source: Reviewer’s results)

5. CONCLUSIONS

From a statistical perspective, the study results support the efficacy of WC3016, 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.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22501

ORIG-1

WARNER
CHILCOTT CO INC

 (b) (4)

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/s/

KATE L DWYER
12/28/2009

MAHBOOB SOBHAN
12/28/2009

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA: 22-501

Applicant: Warner Chilcott Company, Inc.

Stamp Date: 3/26/2009

Drug Name: (b) (4)

45 day Meeting Date: 4/30/2009

Indication: Prevention of Pregnancy

Medical Officer: Ronald Orleans, M.D.

Project Manager: Karl Stiller

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. Based on the data from the study, sponsor's analysis demonstrated that Combination Oral Control (COC) therapy WC3016 provides comparable efficacy and safety results for currently marketed COC therapy.

Brief Summary of Pivotal Phase III Clinical Study for WC3016

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatments	Sample Size (MITT ¹)	Duration of Treatment	Design ²
WC3016 (68 / U.S.) 11-01-06 to 08-27-08	Sexually active females who were at risk of pregnancy with 18-45 years of age and BMI ≤ 35	WC3016	1660 (1582)	thirteen of 28-day cycles of WC3016	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			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
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.

4/30/09

Reviewing Statistician

Date

Mahboob Sobhan, Ph. D.

4/30/09

Supervisor/Team Leader

Date

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/s/

Kate L Dwyer
4/30/2009 02:03:29 PM
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Mahboob Sobhan
5/5/2009 09:37:59 AM
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