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 Serial Number:	50795/S-010
Drug Name:	DORYX (doxycycline hyclate delayed-release tablets, USP) 200 mg tablet
Indication(s):	Treatment of uncomplicated urogenital chlamydia
Applicant:	Warner Chilcott, LLC
PDUFA Date:	11 April, 2013
Review Priority:	Resubmission Class 2
Biometrics Division:	DB IV
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Keywords: Non-inferiority

1. EXECUTIVE SUMMARY

Warner Chilcott, LLC, hereafter referred to as Applicant, resubmits sNDA for a new 200 mg qd WC2031 (doxycycline hyclate delayed-release tablets) for the treatment of uncomplicated urogenital *C. trachomatis* infection. The Applicant filed a formal dispute with OAP on May 23, 2012 in response to the Complete Response letter sent by the Division on July 2011. A dispute resolution meeting was held on June 28, 2012 and Edward Cox, MD, Director of OAP, determined that the results of PR-04809 show that WC2031 is effective, after reviewing the materials the Applicant submitted in support of their appeal, the reviews and decision memoranda prepared by the Division of Anti-infective Products (DAIP) staff, the CR letters, and other pertinent material. He granted the dispute appeal on August 24, 2012 and asked the Applicant to resubmit the sNDA.

After careful review of the data and other pertinent documents (see Statistical review entered into DARRTS on 26 April, 2011 and an addendum to the statistical review was made and entered in DARRTS on August 23, 2012), I believe it is scientifically appropriate to base the primary efficacy analysis on the true *microbiological Intent to Treat* (mITT) analysis, i.e., considering the patients' outcomes based upon available microbiological response documentation and regardless of evaluability and consider patients missing a *C. trachomatis* result as failures. Using these criteria, the microbiological eradication rates are 86.7% for WC2031 and 90.0% for Vibramycin with a 95% CI of (-10.3%, 3.7%). Furthermore, I consider the analyses based on a conservative imputation of non-evaluable patients in the mITT and the 'Per Protocol' as sensitivity analysis. The results of these analyses are driven by differential missing between treatment arms for reasons that may be unrelated to the study drug, although difficult to establish. I come to the conclusion that the drug may be considered non-inferior to Vibramycin using a 10% non-inferiority margin but the 3.3% reduction in treatment effect of WC 2031 from Vibramycin must be conveyed in the label.

2. INTRODUCTION

This application was originally submitted on May 28, 2009 as a supplemental NDA for a new 200 mg qd WC2031 (doxycycline hyclate delayed-release tablets) for the treatment of uncomplicated urogenital *C. trachomatis* infection. It was given a Complete Response letter on September 29, 2009, in which the primary deficiency cited was lack of an approved indication for the 200 mg strength. The Applicant submitted a response which included clinical data conducted through Study PR-04809 "Safety and Efficacy of WC2031 versus Vibramycin for the treatment of Uncomplicated Urogenital Chlamydia trachomatis Infection: A Randomized, Double-blind, Double-dummy, Active-controlled, Multicenter (Phase 3)" to support the use of Doryx to treat C. trachomatis" on November 22, 2010. This trial was designed to evaluate the efficacy and safety of 200 mg WC2031 qd versus 100 mg Vibramycin bid for 7 days, given orally to a total of 495 subjects, for the treatment of uncomplicated urogenital *C. trachomatis* infection. The primary efficacy variable was the proportion of subjects who yielded a negative GP AC2 NAAT test when re-tested 28 days after therapy and with initial positive test (mITT population). Upon review of this supplemental application, the Division issued a Complete Response letter on July 2011 (see also Statistical review entered into DARRTS on 26 April, 2011) citing the following deficiencies:

1. *The results of the clinical trial failed to demonstrate non-inferiority of the new tablet regimen (200 mg tablets taken orally once a day for 7 days) to Vibramycin (100 mg tablets taken orally twice a day for 7 days) for the treatment of uncomplicated urogenital Chlamydia trachomatis (C. trachomatis) infection in the microbiological Intent to Treat (mITT) population. The microbiological cure rate in the mITT population for the WC2031 (200-mg tablet) treatment group was 79.3% versus 83.7% for the Vibramycin reference group with a difference of -4.4%. The lower bound of the 95% confidence interval for the difference in cure rates between treatments was -12.8% which fails to rule out a -10% noninferiority margin. The primary efficacy analysis should be based on mITT as per the statistical analysis plan. However, it was performed and submitted based on the subgroup of mITT patients with evaluable efficacy outcomes. This analysis excluded 32 (17.0%) non-evaluable patients in the WC2031 arm and 23 (12.1%) nonevaluable patients in the Vibramycin arm. Because the approach constitutes a subgroup analysis, it lacks randomization protection and the results are potentially biased.*
2. *Even if Study PR004809 had demonstrated non-inferiority based on a margin of -10%, the non-inferiority margin justification is inadequate because of concerns regarding the timing of the test-of-cure visit. Specifically, the natural history studies in your IND submission dated February 3, 2010 had variable timing of repeat C. trachomatis testing, so it is not clear that the high rate of positive testing would be sustained at day 28 for untreated patients. Further, it is not clear whether all available literature regarding untreated or inadequately treated C. trachomatis infections has been considered in providing your noninferiority margin justification.*

Post-action meetings in response to these deficiencies were held on August 29, 2011 and January 24, 2012 and the Applicant filed a formal dispute in response to the Complete Response with OAP on May 23, 2012 on the following basis:

1. *Subsequent to receiving a Complete Response for our sNDA submission [new 200mg tablet strength of Doryx] on September 29, 2009, Warner Chilcott sought Agency guidance at a January 19, 2010 Type C Meeting. The Sponsor received and implemented the subsequent recommendations of the Division, as we understood them, in the design of the study protocol, non-inferiority (NI) margin justification, literature searches, ITT population, and statistical analysis plan.*
2. *The primary analysis, as specified in the prospectively defined statistical analysis plan for the study, showed microbiological cure rates in the mITT population without imputations of 94.9% and 94.6% for the Test and Reference drugs, respectively, and a 2-sided 95% confidence interval on the difference between cure rates -4.6% to 5.1 %. The confidence interval meets conservative criteria for a demonstration of non-inferiority and suggests that the two treatment regimens are in fact equivalent.*
3. *Warner Chilcott provided additional information to FDA in response to a request regarding Primary Analysis Population, submitted February 2, 2010, in which specific scenarios and their resulting values were presented. We also noted that no imputations were to be made for nonevaluable outcomes, as these would be "included" as missing values, but a separate sensitivity analysis would be performed and provided on all non-*

evaluable outcomes. Additionally, we highlighted that the protocol would be revised to indicate that the primary analysis would be conducted in the modified ITT population of randomized subjects with C. trachomatis infection at baseline who received at least one dose of the study medication.

4. *Warner Chilcott provided additional information to FDA in response to a request regarding Test of Cure, submitted February 5, 2010, in the form of a White Paper supporting the justification for a 28-day TOC, including a copy of all literature references. This white paper detailed the rationale for performing the TOC at day 28 using a nucleic acid amplification test (NAAT).*
5. *A thorough investigation of the robustness of the conclusions with respect to possible imputations for the 55 subjects (14.6%) who failed to provide a test of cure in the study was submitted to the Agency as part of the Meeting Package for an August 29, 2011 Type C meeting. The analysis showed that the confidence interval remained within the prospectively defined 10% NI margin under all plausible imputations. Contained within the clinical study report were the results of four imputation rules, only one of which was selected by the Division for primary consideration in its review of the study results. In this analysis, it was assumed that all outcomes classified as nonevaluable were treatment failures. Warner Chilcott believes that it is scientifically incorrect to base the entire weight of evidence from this clinical trial with respect to the important determination of noninferiority on this single extreme imputation rule, which introduces an unfair bias against the Test treatment. The Division has declined to engage in a discussion of the scientific merits of this analysis.*
6. *The Division's determination that the study results failed to demonstrate noninferiority appears to rest entirely on the most conservative particular imputation method, in which all 55 subjects with missing data are considered to have failed treatment. Interpreting the study outcome by exclusive focus on this single extreme imputation method, not assigned a primary role in the prospective statistical analysis plan, and refusing to consider the weight of evidence to the contrary interpretation, is not appropriate.*

On June 28, 2012, a meeting was held for dispute resolution. In this meeting, the applicant provided additional information regarding the statistical analysis plan, determination of non-evaluable subjects, and justification of the non-inferiority margin. An addendum to the statistical review was made and entered in DARRTS on August 23, 2012. In this addendum, the outcomes for the 56 non-evaluable cases were re-assessed based on a clinical review of each of the 56 case report forms. When these indeterminates are considered as failures, the microbiological eradication rate in the mITT population for the WC2031 treatment group is 82.4% versus 86.8% for the Vibramycin reference group. The 95% confidence interval for the difference in eradication rates between treatments was (-11.5%, 3.8%). On the other hand, when they are considered as successes, the microbiological eradication rate in the mITT population for the WC2031 treatment group is 85.1% versus 87.9% for the Vibramycin reference group with the 95% confidence interval for the difference in eradication rates as (-9.6%, 5.0%).

Edward Cox, MD, Director of OAP, reviewed the materials that the Applicant had submitted in support of their appeal that include the reviews and decision memoranda prepared by the Division of Anti-infective Products (DAIP) staff, the CR letters, and other pertinent material, and also considered the discussions of our June 28, 2012 meeting and the review of the additional

information submitted on July 13 and August 8, 2012. He determined that the results of Study PR-04809 "Safety and Efficacy of WC2031 versus Vibramycin for the treatment of Uncomplicated Urogenital Chlamydia trachomatis Infection: A Randomized, Double-blind, Double-dummy, Active-controlled, Multicenter (Phase 3)" show that WC2031 is effective and granted the dispute appeal on August 24, 2012.

3. STATISTICAL EVALUATION

There are no new data in this resubmission. The following are some re-analysis of data from the review of the supplement, the addendum and additional information provided by the Applicant during the formal dispute resolution.

3.1. Evaluation of Efficacy

3.1.1 Efficacy Outcome

At the Day 28 visit, the proportion of subjects in the mITT population with microbiological cure, defined as a negative result for urogenital *C. trachomatis* on the GP AC2 NAAT for the WC2031 treatment group was 79.3 % versus 83.7% for the Vibramycin reference group. The 95% confidence interval for the difference in cure rates between treatments was (-12.8%, 3.9%). The mITT population defined here consisted of all randomized subjects who had a positive NAAT for *C. trachomatis* at the Baseline visit and took at least one dose of study drug. Patients who considered as non-evaluable were imputed as failures.

Table 1: Efficacy outcome - Microbiological Eradication of *C. trachomatis* at Day 28; mITT Population

mITT Primary Analysis	Applicant Analysis			FDA Analysis		
	WC2031	Vibramycin	Difference	WC2031	Vibramycin	Difference
N	157	168		188	190	
Microbiological Eradication	149 (94.9)	159 (94.6)	0.3	149 (79.3)	159 (83.7)	-4.4
95% Confidence Interval for Eradication Rate			-4.6, 5.1			-12.8, 3.9

The Applicant reported an analysis which is based on a subgroup of the mITT population with evaluable efficacy outcomes, i.e., this subgroup excludes all the non-evaluable patients so that the sample considered is just a subset of the original mITT population. The microbiological eradication rate in the mITT population for the WC2031 treatment group was 94.9% versus 83.7% for the Vibramycin reference group. The 95% confidence interval for the difference in cure rates between treatments was (-4.6%, 5.1%). There are several limitations with this subgroup analysis that excludes patients based on post-randomization selection.

The mITT population, in which patients are excluded, based only on the results of the baseline assessment of pathogens is the appropriate primary analysis. However, the imputation of failure for outcomes that were available for some patients, but only that they are not evaluable due to reasons other than being missing, maybe conservative. On the other hand, the analysis where subjects are excluded due to non-compliance with the study protocol is generally considered a "Per Protocol" analysis protocol. Due to the fact that this subset of patients may no longer have the protection against bias due to imbalances between treatment groups, it is generally

considered appropriate for secondary analyses or supportive analyses but not as primary analyses even if the protocol specified primary analysis population does appear to be the population that excludes individuals for a number of reasons, including missing outcome data.

Table 2: Efficacy outcome: Missing observations as failures and non-evaluable outcomes taken at face value.

mITT Primary Analysis	Applicant Analysis			FDA Analysis		
	WC2031	Vibramycin	Difference	WC2031	Vibramycin	Difference
N	188	190		188	190	
Microbiological Eradication	163 (86.7)	171 (90.0)	0.3	163 (86.7)	171 (90.0)	-3.3
95% Confidence Interval for Cure Rate			-9.8, 3.2			-10.3, 3.7

As a trade-off between these two analyses, we considered an analysis on the mITT population based on the idea that patients should be analyzed in the groups to which they were randomized and with the target pathogens, but regardless of whether they received or adhered to the protocol. As such, missing observations were considered failures while the outcome of non-evaluable patients is based on what was observed. The microbiological eradication rate in this population for the WC2031 treatment group was 86.7% versus 90.0% for the Vibramycin reference group. The 95% confidence interval for the difference in cure rates between treatments was (-10.3, 3.7) as shown in Table-2. This confidence interval uses the Wilson's method with continuity correction in contradistinction to the use of normal approximation and multiple imputation strategy based on 500 imputation sets. Multiple imputations use assumptions that are untestable and this analysis was performed post hoc by the Applicant.

Table 3: Reasons for non-evaluable subjects

Reason not evaluable	Number of Subjects	
	WC2031	Vibramycin
Group A		
Lost to follow-up after baseline	10	5
Withdrew consent (too busy, schedule conflicts, personal reasons)	3	0
Adverse reactions, test not performed	1	2
Completed subject, test not performed	3	3
Took excluded meds, cured in window	3	2
Other Protocol deviations, not cured in window	1	2
Other Protocol deviations, test not performed	0	1
Group B		
Adverse reactions, but cured	1	0
Non compliant with study meds, but cured in window	1	2
Early EOS visit, but cured	1	1
Other Protocol deviations, cured in window	4	3
Group C		
Late EOS visit, but classified as cured	5	2
Total non-evaluable	**33**	**23**

In the first two analyses, the impact of the non-evaluable data is driving the difference in the two analyses at opposite ends and, consequently, the non-inferiority conclusion. So we investigated the Case Report Forms of the 56 non-evaluable subjects to determine their appropriate endpoint classification. Table-3 provides a breakdown of the reasons for non-evaluability in the two groups. In this table, the non-evaluable outcomes Group A are assigned as failures, while those

with reasons in Group B are assigned as successes. The non-evaluable outcomes in Group C are assigned an indeterminate and will be assigned either a failure or success in the sensitivity analysis.

If the outcomes for patients (n=7) in Group C (late EOS visit) are considered as failures, the microbiological eradication rate in the mITT population for the WC2031 treatment group is 82.4% versus 86.8% for the Vibramycin reference group, as shown in Table-4. The 95% confidence interval for the difference in cure rates between treatments was (-11.5%, 3.8%). On the other hand, when they are considered as successes, the microbiological cure rate in the mITT population for the WC2031 treatment group is 85.1% versus 87.9% for the Vibramycin reference group with the 95% confidence interval for the difference in eradication rates as (-9.6%, 5.0%). As a worst case scenario, if the outcomes in the WC2031 arm are classified as failure and success for the Vibramycin arm, the microbiological cure for the WC2031 treatment group is 82.4% versus 87.9% for the Vibramycin reference group. The 95% confidence interval for the difference in cure rates between treatments was (-12.5%, 2.6%).

Table 4: Sensitivity Analysis based on the imputed outcome of patients in Group C

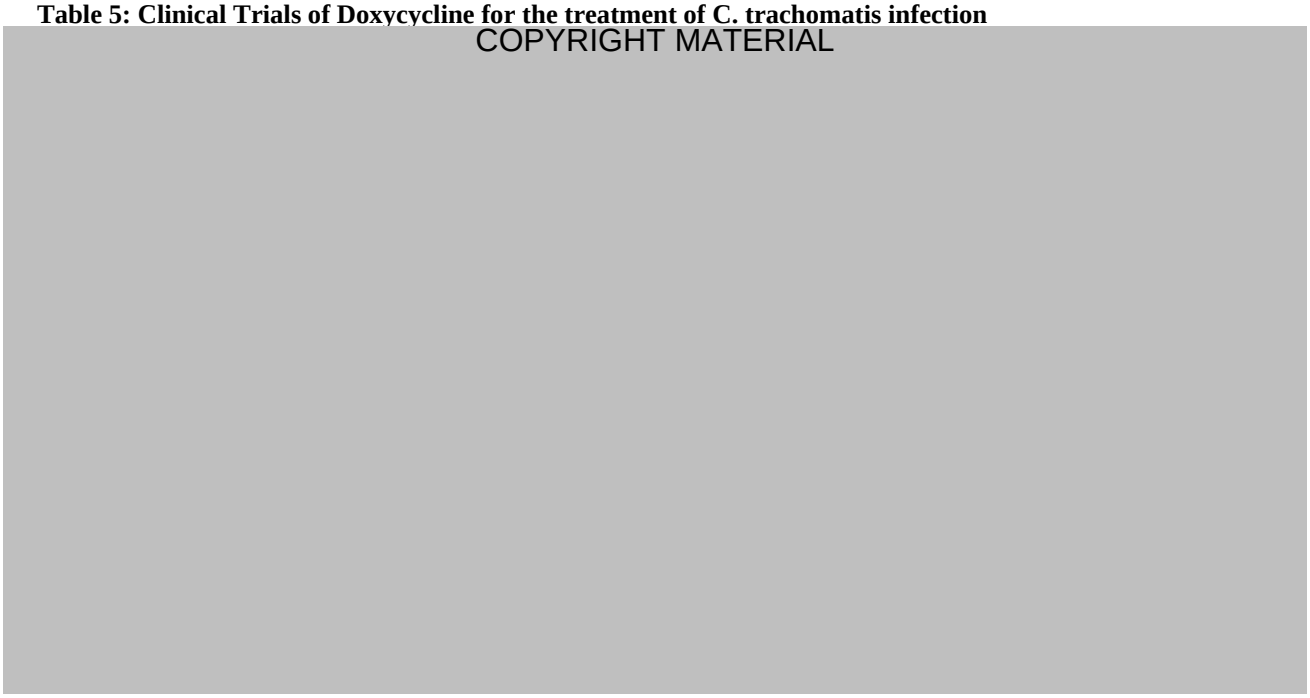
mITT Primary Analysis	**WC2031**	**Vibramycin**	**Difference (95% CI)**
N	**188**	**190**	
Late EOS classified as failure			
Microbiological Cure	156 (82.4)	165 (86.8)	-3.9
95% Confidence Interval			-11.5%, 3.8%
Late EOS classified as success			
Microbiological Cure	161 (85.1)	167 (87.9)	-2.3
95% Confidence Interval			-9.6%, 5.0%
Late EOS considered failure for WC2031 and success for Vibramycin			
Microbiological Cure	156 (82.4)	167 (87.9)	-4.9
95% Confidence Interval			-12.5%, 2.6%

Multiple imputation procedures using prognostic factors such as age and sex give a treatment difference of -0.47% [95% CI: -5.6, 4.8]. Hence the treatment difference hovers from -0.47% to -3.9% [95% LCLs from -5.6 to -12.5].

3.1.2 Non-inferiority margin

Several studies demonstrate that spontaneous clearance of *C. trachomatis* in infected laboratory animals suggest that untreated infection may resolve simultaneously. Resolution is also associated with longer intervals between the time of testing and treatment (Parks et al., 1997). Parks et al. also reported that in a study of 74 patients with positive Chlamydial culture, 21 of the 74 patients (28%; 95% CI: 18.8, 40.2) yielded a negative test using PCR methods when re-tested 4 to 45 days after the initial positive test, with patients having undergone no treatment for the infection in the interval. The proportion of subjects reverting to a negative test was somewhat smaller among patients re-tested less than 21 days after the initial test (15/64, 23%). Over 70% of the observed patients had persistent Chlamydia infection either from re-infection or colonization.

Table 5: Clinical Trials of Doxycycline for the treatment of C. trachomatis infection



Reproduced from Lau et al (2002)

Lau et al., on the other hand, performed a meta-analysis of 12 randomized clinical trials (see Table-5) investigating the efficacy of azithromycin and doxycycline in the treatment of genital chlamydial infections and reported that the microbiological cure rates ranged from 81% to 100% and showed no significant differences between the treatments with respect to efficacy. The average cure rate for doxycycline was 98%. Considering only 4 double-blind studies having similar time of assessment as the current study (see shaded rows of Table-5), the resulting treatment effect of doxycyline is 93.5% (95% CI: 89.6, 96.1).

Based on these information, the historical evidence of sensitivity to drug effect can be calculated conservatively 90% - 40% = 50%. Since the data on spontaneous resolution rate is based on observational studies, one can also use the upper limit of 99% CI around the treatment response [28.38, 99% CI: (15.98, 43.64)] so that M1 = 90% - 44% = 46%. Given that over 70% of observed patients had persistent Chlamydia infection, it is likely that the no treatment response is about 44% and perhaps even higher in men. Nevertheless, the data support that the treatment effect of the active control is in excess of 10% and the assessment of what margin to use becomes an issue of what level of treatment effect one is willing to give up when evaluating the test treatment. Such an assessment can be based on the determination of a clinically irrelevant effect and the integrity of the data.

Note that the no-treatment rate was estimated using a single non-comparative study in which the patients were re-tested anywhere from 4 to 45 days after the initial positive test. Given that spontaneous resolution of the infection follows a time-dependent manner, it poses restrictions to the capability to ascertain the true placebo rate. The study also has limitations due to the fact that *C. trachomatis* culture methods vary from laboratory from laboratory and that it used culture or

PCR based testing, for which sensitivity and specificity are not high and hence, less reliable. Male specimens in this study are also scarce.

3.2 Evaluation of Safety

See Medical Officers review and the original Statistical review entered into DARRTS on 26 April, 2011.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

See original Statistical review entered into DARRTS on 26 April, 2011.

5. CONCLUSION

I reckoned that it is scientifically appropriate to perform the primary efficacy analysis on the true mITT analysis, i.e., consider the patients' outcomes based upon available information and regardless of evaluability and consider patients missing a *C. trachomatis* result as failures. The results for this analysis are 86.7% for WC2031 and 90.0% for Vibramycin with a 95% CI of (-10.3%, 3.7%) while the analyses based on a conservative imputation of non-evaluable patients in the mITT results are 79.3% for WC2031 and 83.7% for Vibramycin with a 95% CI of (-12.8%, 3.9). The 'Per Protocol' analysis yields 94.9% for WC2031 and 94.6% for Vibramycin with a 95% CI of (-4.6%, 5.1%). Although this analysis is not an appropriate primary analysis population, in the subgroup of patients that do comply with the study procedures the outcomes are numerically similar between treatment arms. Other sensitivity analysis based on classification of patients in Group C (see Table-5) has the treatment difference hovering from -2.3% to -3.9% [95% LCLs from -9.6 to -11.5]. Because the sensitivity analysis shown in this table are re-assessments of the data which have already been unblinded, it can only be considered as supportive analyses to the original mITT analysis given in Table-2.

Only a single patient result can switch the significance of the mITT result (see Table-2) and that this result is driven by differential missing between treatment arms. Examination of the reasons that subjects were non-evaluable finds that there are differences in the categories of "loss to follow-up" of 10 patients for WC2031 and 5 patients for Vibramycin and "withdrew consent" of 3 patients for WC2031 and 0 patients for Vibramycin are affecting the trial results but that none of these reasons seem related to the study drug. So, I come to the conclusion that the drug maybe considered non-inferior to Vibramycin at the 10% non-inferiority margin but the 3.3% reduction in treatment effect of WC 2031 from Vibramycin must be conveyed in the label so that healthcare providers and patients will have such information available.

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