CLINICAL REVIEW

Application Type	505(b)(2) Efficacy Supplement, Resubmission/Class 2
Application Number	NDA 50-795/S-010
Priority or Standard	Standard
Submit Date	October 08, 2012
Received Date	October 11, 2012
PDUFA Goal Date	April 11, 2013
Division / Office	Division of Anti-Infective Products/OND
Reviewer Name	Dmitri Iarikov, MD
Review Completion Date	March 14, 2013
Established Name	Doxycycline Hyclate
(Proposed) Trade Name	Doryx®
Therapeutic Class	Tetracycline
Applicant	Warner Chilcott (US) LLC
Formulation	200 mg oral tablet
Dosing Regimen	One 200-mg tablet once a day
Indication	Uncomplicated Urogenital *Chlamydia trachomatis* Infection
Intended Population	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The review of this efficacy supplement, class 2 resubmission concludes that doxycycline 200 mg tablets (WC2031) can be approved for the treatment of uncomplicated urogenital *C. trachomatis* infection.

A complete response letter was issued by the Agency on July 1, 2011 when the FDA concluded that WC2031 failed to demonstrate non-inferiority for the treatment of uncomplicated urogenital *C. trachomatis* infection when compared with Vibramycin 100 mg tablets in a phase 3 double-blind randomized clinical trial. This was contrary to the Applicant's analyses that concluded non-inferiority of WC2031 and the comparator.

After the Applicant requested formal dispute resolution, the FDA conducted additional analyses of outcomes in subjects that initially were considered non-evaluable and concluded that WC2031 met criteria for non-inferiority when compared with Vibramycin and granted the dispute appeal.

1.2 Risk Benefit Assessment

The 200 mg doxycycline hyclate tablet (WC2031) taken once a day for 7 days for treatment of uncomplicated urogenital *C. trachomatis* infection demonstrates similar efficacy as compared with the reference treatment regimen of the 100 mg doxycycline hyclate tablet taken twice a day for 7 days. No specific safety concerns related WC2031 have been identified in. Moreover, fewer treatment-related adverse events, including nausea and vomiting were observed in the WC2031 than in the comparator arm.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

WC2031 is a new 200-mg strength tablet of doxycycline hyclate, a tetracycline antibacterial, which is specifically proposed for the treatment of *Chlamydia trachomatis* infections.

Doxycycline is a tetracycline antibacterial which inhibits bacterial protein synthesis by binding reversibly to the 30S unit of bacterial ribosome and preventing addition of amino acids to the growing peptide. The half-life of doxycycline ranges from 18 to 22 hours which allows its once daily dosing. Doxycycline is nearly completely absorbed after oral administration.

2.2 Tables of Currently Available Treatments for Proposed Indications

- Azithromycin by mouth one single 1 gram dose
- Doxycycline hyclate by mouth 100 mg twice daily for 7 days
- Demeclocycline hydrochloride by mouth in 4 divided doses of 150 mg each or 2 divided doses of 300 mg each; duration is not specified in the labeling
- Erythromycin by mouth 800 mg three times a day for 7 days
- Minocycline hydrochloride by mouth 100 mg every 12 hours for at least 7 days
- Ofloxacin by mouth 300 mg every 12 hours for 7 days
- Tetracycline hydrochloride by mouth 500 mg four times a day for at least 7 days

2.3 Availability of Proposed Active Ingredient in the United States

Doxycycline hyclate is available as (b) (4) 100 mg, and 150 mg oral tablets. With this efficacy supplement, the applicant is proposing to market an additional 200-mg tablet strength.

2.4 Important Safety Issues with Consideration to Related Drugs

The most recent changes to the labeling relevant to the drug safety and efficacy were made in March 2011 when skin related adverse reactions were added to the ADVERSE REACTIONS section, subsection *6.2 Skin*. The following information was added:

Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Exfoliative dermatitis has been reported but is uncommon.

The use of drugs of tetracyclines during the last half of pregnancy and to the age of 8 years may cause permanent yellow-gray-brown discoloration of the teeth. Tetracyclines can also cause retardation of skeletal development in the fetus when administered to a pregnant woman.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An initial supplemental New Drug Application (sNDA) proposing a new 200 mg tablet strength of Doryx (doxycycline hyclate) tablets (a.k.a. WC2031) was a manufacturing supplement, submitted on May 29, 2009. In support of the submission the Applicant provided results of two clinical pharmacology studies. A bioequivalence study demonstrated that one 200 mg tablet is bioequivalent to two 100 mg tablets. The second study demonstrated that the pharmacokinetics of doxycycline 200 mg tablet is not altered by food intake.

However, the manufacturing supplement received a Complete Response from the Agency on September 29, 2009 indicating following deficiencies:

- There is no approved indication and dosage that uses 200 mg as a dose.
- Having a tablet strength on the market with no approved dosage regimen will lead to medication errors and potential off-label use.

The FDA recommended that the applicant provide data demonstrating the safety and effectiveness of doxycycline using a 200 mg dose regimen and include the proposed indication in product labeling.

After receiving the complete response letter the Applicant conducted a phase 3 study titled “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 Study,” protocol number PR-004809 and resubmitted the sNDA on November 22, 2010.

The trial was conducted at 44 centers in the United States between April, 2010 and October, 2010. For the full analysis of the trial the reader is referred to the NDA efficacy supplement review by Dr. Modelina Nasim dated June 13, 2011. Of note, no safety concerns regarding WC2031 had been identified.

The primary objective of the trial was to evaluate the clinical efficacy and safety of WC2031 taken orally once a day for 7 days versus Vibramycin 100 mg (doxycycline hyclate tablets) taken orally twice a day for 7 days for the treatment of uncomplicated urogenital *C. trachomatis* infection. The primary outcome was the proportion of subjects with microbiological cure at the Day 28 visit, defined as a negative result for urogenital *C. trachomatis*. This was a noninferiority trial and the applicant provided a justification for a non-inferiority margin of 10%.

The Applicant performed the primary efficacy analysis in subjects with evaluable efficacy outcomes. Non-evaluability was based on *C. trachomatis* tests outside the evaluation window, non-compliance with study medication, receipt of exclusionary treatment, or missing Day 28 *C. trachomatis* result. This analysis showed that the microbiological cure rate for the WC2031 arm was 94.9% versus 83.7% for the Vibramycin arm. The 95% confidence interval (CI) for the difference in cure rates between treatments was (-4.6%, 5.1%).

However, FDA noticed that this represents a subgroup analysis because it excluded 32 (17.0%) non-evaluable patients in the WC2031 arm and 23 (12.1%) non-evaluable patients in the Vibramycin arm and pointed out that this subgroup lacks randomization protection and was potentially biased. FDA indicated that the primary efficacy analysis should have been based on the modified ITT (mITT) population, consisting of all randomized subjects who tested positive for *C. trachomatis* at the baseline visit and took at least one dose of study drug. Cure rate in this analysis was 79.3% versus 83.7% for the WC2031 and Vibramycin groups, respectively, with a difference in cure rates between treatments of -4.4% and the lower bound of the 95% CI for the difference of 12.8% which fails to rule out a (-10%) noninferiority margin. Therefore, in its initial assessment the FDA concluded that WC2031 failed to demonstrate non-inferiority for the treatment of uncomplicated urogenital *C. trachomatis* infection when compared to Vibramycin and issued the Complete Response letter on July 1, 2011.

On May 23, 2012 the applicant submitted a request for formal dispute resolution asking for re-consideration of Study PR-04809. In summary, the request indicates that the demonstration of non-inferiority of WC2031 in subjects with evaluable efficacy was the pre-specified primary efficacy outcome whereas the FDA's decision to evaluate the outcome in the analysis when all non-evaluable outcomes are considered as treatment failures introduces an unfair bias against the test treatment.

On August 24, 2012 the Agency granted the dispute appeal.

As a part of dispute resolution process, the Agency requested for additional review a total of 56 case report forms of subjects whose outcome was identified as non-evaluable during the initial review. Consequently, the FDA evaluated the results of the trial based on what it finds to be a more appropriate analysis population. In this analysis subjects with missing Day 28 *C. trachomatis* results were considered failures while subjects with documented cure and accepted protocol deviations were considered cures. The cure rate in the mITT population for the WC2031 group was 86.7% versus 90.0% for the Vibramycin group with a difference of -3.3% and the 95% confidence interval for the difference in cure rates between treatments was (-10.3%, 3.7%). Please see section 6 of this review for more details.

The dispute appeal-granted letter acknowledges that the primary analysis population specified in the protocol does appear to be the population that excludes individuals for a

number of reasons, including missing outcome data. This 'Efficacy Evaluable' population based analysis finds a microbiological cure rate of 94.9 % for WC2031 and 94.6% for Vibramycin (95%CI -4.6, 5.1).

The letter also indicates that the analysis results presented in the FDA Complete Response letter of July 1, 2011 of a microbiological cure rate of 79.3% for WC2031 and 83.7% for Vibramycin with a 95% CI of (-12.8%, 3.9%) are more appropriately considered as a sensitivity analysis. These analyses were based on the micro-ITT population, as appropriate, but the imputation of outcomes that were not missing for some patients (namely, patients excluded from the Efficacy Evaluable population for reasons other than missing outcome data) represents an extreme case.

FDA indicated that while the per protocol 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. The difference between efficacy analyses in the mITT and Efficacy Evaluable populations is due to an imbalance in missing data between treatment groups.

The letter also indicates that it will be important to provide the results of the mITT analysis in product labeling so that healthcare providers and patients will have such information available. The FDA suggested that the Applicant re-submit their supplemental NDA to the Division of Anti-Infective Products. On October 8, 2012 the Sponsor re-submitted NDA 50-795 / S-010 which is the subject of this review.

3 Ethics and Good Clinical Practices

Since this resubmission includes efficacy re-analyses of the clinical trial already evaluated during the initial NDA submission, no additional ethics and good clinical practices evaluations were needed. Submission was provided as PDF files and was overall well organized.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See section 5.2 Review Strategy

4.2 Clinical Microbiology

See section 5.2 Review Strategy

4.3 Preclinical Pharmacology/Toxicology

See section 5.2 Review Strategy

4.4 Clinical Pharmacology

See section 5.2 Review Strategy; a brief summary of the pharmacologic properties of doxycycline hyclate is provided in section 2.1 Product Information of this review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical program for WC2031 (doxycycline hyclate 200 mg tablets) consisted of 3 clinical pharmacology trials and 1 active-controlled safety and efficacy trial. This review will analyze the results of the efficacy trial.

Clinical pharmacology studies are listed below for completeness sake:

- Study PR-02108 compared the bioavailability of doxycycline following single-dose oral administration of one WC2031-200 tablet versus two WC2031-100 tablets.
- Study PR-02308 determined the effect of food on doxycycline bioavailability following oral administration of a single WC2031-200 tablet in healthy volunteers.
- Study PR-06410 characterized doxycycline bioavailability following multiple-dose oral administration.

The efficacy trial was a multicenter, double-blind, double-dummy active control study to evaluate the efficacy and safety of WC2031 200 mg tablets taken orally once a day for 7 days versus doxycycline hyclate tablets 100 mg tablets taken orally twice a day for 7 days, in the treatment of uncomplicated urogenital *C. trachomatis* infection, study PR-04809. The trial was conducted in 44 centers in the United States between April, 2010 and October, 2010.

5.2 Review Strategy

This review re-evaluates the efficacy results of study PR-04809 after treatment outcomes of 56 subjects (previously considered non-evaluable) were adjudicated. This analysis aimed to increase the size of analyzable mITT population in order make more informative conclusions on the efficacy of WC2031 200 mg tablets.

No new safety data have been generated since the evaluation of safety of WC2031 was conducted by Dr. Nasim Modelina in her June 2011 efficacy supplement review. Therefore, while the summary of safety information will be provided herein, the reader is

referred to Dr. Modelina's review for more details. The same is pertinent to chemistry manufacturing and controls, clinical microbiology, preclinical pharmacology/toxicology, and clinical pharmacology evaluations where the reader is referred to the respective reviews.

5.3 Discussion of Individual Studies/Clinical Trials

As indicated above, the review is focused on the pivotal trial titled "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 Study", protocol number PR-04809.

In this trial WC2031 200-mg tablets were taken orally once a day for 7 days versus doxycycline hyclate 100-mg tablets taken orally twice a day for 7 days. The trial was conducted in 44 centers in the United States between April, 2010 and October, 2010.

The plan was to enroll about 480 subjects with the intent to have approximately 200 subjects per group available for the primary efficacy analyses. The 20% rate of exclusion was to account for the subjects with a negative test for *C. trachomatis* at baseline.

Selected inclusion criteria were as follows:

- 19 to 45 years of age, inclusive, at baseline
- Confirmed diagnosis of urogenital *C. trachomatis* infection <14 days prior to enrollment or partner(s) of a subject with a known positive test for urogenital *C. trachomatis* infection

Selected exclusion criteria were as follows:

- Clinical diagnosis of pelvic inflammatory disease or epididymitis at the baseline visit
- Known diagnosis of *N. gonorrhoea*
- Known HIV infection
- Known active Hepatitis B or C infection
- Known intolerance or hypersensitivity to the tetracycline class of antibiotics
- Prior hysterectomy (partial or total)
- Treatment with an antimicrobial therapy with known activity against urogenital *C. trachomatis* within 28 days of the positive test for study enrollment (e.g., macrolides, tetracyclines, quinolones, penicillins, cephalosporins, and clindamycin)

Each subject was randomly assigned to 1 of the 2 following treatments in a ratio of 1:1

- WC2031 tablet, 200 mg PO daily for 7 days
- Vibramycin tablet, 100 mg PO twice a day for 7 days

The trial included 3 clinic visits:

1. Day 1 Baseline (randomization and initiation of treatment)
    - For female subjects, the following tests were performed:
      a) Urine pregnancy test
      b) Vaginal swab for:
        - GP AC2 NAAT to test for urogenital *C. trachomatis* and *N. gonorrhoeae*
        - PCR to test for *M. genitalium*
      c) Vaginal wet mount to test for *T. vaginalis*, Candidiasis, and bacterial vaginosis
    - For male subjects, the following tests were performed after the first void urine:
        - GP AC2 NAAT to test for *C. trachomatis* and *N. gonorrhoeae*
        - PCR to test for *T. vaginalis* and *M. genitalium*

2. Day 8 (-1/+3 days) End-of-Treatment [EOT]
    - Urine pregnancy test

3. Day 28 (-3/+7 days) End-of-Study [EOS] / Test-of-Cure [TOC]
    - For female subjects, the following tests were performed:
      a) Vaginal swab for:
        - GP AC2 NAAT to test for urogenital *C. trachomatis* and *N. gonorrhoeae*
        - PCR to test for *M. genitalium*
      b) Vaginal wet mount to test for *T. vaginalis*, Candidiasis, and bacterial vaginosis
    - For male subjects, the following tests were performed after the first void urine:
        - GP AC2 NAAT to test for *C. trachomatis* and *N. gonorrhoeae*
        - PCR to test for *T. vaginalis* and *M. genitalium*

The primary efficacy endpoint was the proportion of subjects with microbiological cure at the Day 28 visit, defined as a negative result for urogenital *C. trachomatis* on the GP AC2 NAAT.

For each subject, the evaluability of the GP AC2 NAAT test result for urogenital *C. trachomatis* was determined. The microbiological outcome was considered non-evaluable if:

1. The *C. trachomatis* NAAT test result was missing or outside of the allowable window (Study Day 21 to 42)
2. The subject was less than 80% compliant with study medication or duration of treatment was less than 6 days

3. The subject received exclusionary treatment that has an impact on test-of-cure
4. The subject had any other major protocol deviation known to influence the efficacy outcome

As sensitivity analyses, the non-inferiority test on the primary efficacy variable was repeated using rules of imputation for missing data. All sensitivity analyses were based on the mITT population. The following three sensitivity analyses were performed:

a. alternate Day 28 allowable window, defined as Day 25 to Day 35 (-3/+7 days)
b. all non-evaluable outcomes were included as treatment failures
c. all non-missing outcomes were included regardless of evaluability

After the study was unblinded, an additional sensitivity analysis for the primary efficacy variable was performed. This analysis was in addition to the 3 other pre-specified ones. For this analysis (Sensitivity Analysis 4), all non-missing outcomes were included in the analysis regardless of evaluability, and all missing outcomes were included as treatment failures.

Secondary efficacy assessments included:

- The proportion of subjects with both a microbiological cure (defined as a negative result for urogenital *C. trachomatis*, determined by the GP AC2 NAAT) and a clinical cure (for males defined as resolution of baseline signs/symptoms of dysuria, urethral pruritus and urethral discharge, and resolution of examination finding of urethral discharge; for females, resolution of examination finding of endocervical discharge) at Day 28
- The proportion of subjects in the *M*. *genitalium* co-infected population with microbiological cure for both *M*. *genitalium* and *C. trachomatis* at Day 28, defined by a negative PCR for *M*. *genitalium* and a negative GP AC2 NAAT for *C. trachomatis*
- The proportion of subjects in the *N. gonorrhoeae* co-infected population and in the *N. gonorrhoeae* negative population with microbiological cure for *C. trachomatis* at Day 28, defined by the GP AC2 NAAT.

Subject populations

- The modified ITT (mITT) population 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.
- The safety population included all randomized subjects who took at least one dose of study drug.
- The clinically evaluable population:
  - Males: all mITT subjects who had positive urogenital examination findings (observed or reported) for at least one sign/symptom of dysuria, urethral pruritus or urethral discharge at baseline.
  - Females: all mITT subjects who had positive examination finding for endocervical discharge at baseline.

A non-inferiority margin was selected at 10%. This NI margin was based on the published cure rates of urogenital *C. trachomatis* with doxycycline in this target population of 90 to 98% and historical observations of untreated patients with C. trachomatis (documented by culture) suggesting spontaneous resolution only in up to 54% of these untreated individuals.

6 Review of Efficacy

Efficacy Summary

This review concludes that WC2031 may be considered non-inferior to Vibramycin for the treatment of uncomplicated urogenital *Chlamydia trachomatis* infection.

The reassessment of efficacy outcomes in the mITT population in the phase 3 trial comparing WC2031 and Vibramycin demonstrates a treatment difference of minus 3.3% (95% CI: -10.3, 3.7) between the WC2031 and Vibramycin groups. Of note, the Applicant's analysis demonstrates the same treatment difference of minus 3.3% but with 95% CI of -9.8, 3.2. The differences in the confidence intervals are due to different methods used for confidence interval calculations (more details are provided in section 6.1.3 Analysis of Primary Endpoint(s); the reader is also referred to the statistical review for further details).

In the subgroup of patients that comply with the study procedures the treatment difference is 0.3% (95% CI:-4.6, 5.1). The difference between efficacy analyses in the mITT and Efficacy Evaluable populations is seemingly due to an imbalance in missing data between treatment groups which does not seem to be related to study drug.

6.1 Indication

6.1.1 Demographics

Table 1: Summary of Demographics; Safety Population

Characteristic	WC2031 (N=246)	Vibramycin (N=248)	Total (N=494)
Age (years)			
N	246	248	494
Mean	24.5	24.4	24.5
Median	23	23	23
Minimum, Maximum	19, 43	19, 45	19, 45
Age Group – n (%)			
Less than 30 years	206 (83.7)	216 (87.1)	422 (85.4)
30-40 years	35 (14.2)	29 (11.7)	64 (13)
Greater than 40 years	5 (2)	3 (1.2)	8 (1.6)

Gender – n (%)			
Male	112 (45.5)	111 (44.8)	223 (45.1)
Female	134 (54.5)	137 (55.2)	271 (54.9)
Race – n (%)			
White	81 (32.9)	88 (35.5)	169 (34.2)
Black	138 (56.1)	144 (58.1)	282 (57.1)
Asian	5 (2)	3 (1.2)	8 (1.6)
American Indian of Alaskan Native	3 (1.2)	1 (0.4)	4 (0.8)
Native Hawaiian or Other Pacific Islander	4 (1.6)	1 (0.4)	5 (1)
Multi-Racial	15 (6.1)	11 (4.4)	26 (5.3)
Source: S-010 Resubmission Volume 15; Summary Tables; Modified from Table 14.1.3			

6.1.2 Subject Disposition

A total of 504 subjects were screened of which 9 subjects were screen failures. Of the remaining 495 subjects, 247 subjects were randomized to the WC2031 and 248 subjects to the Vibramycin reference groups, Figure 1 and Table 2.

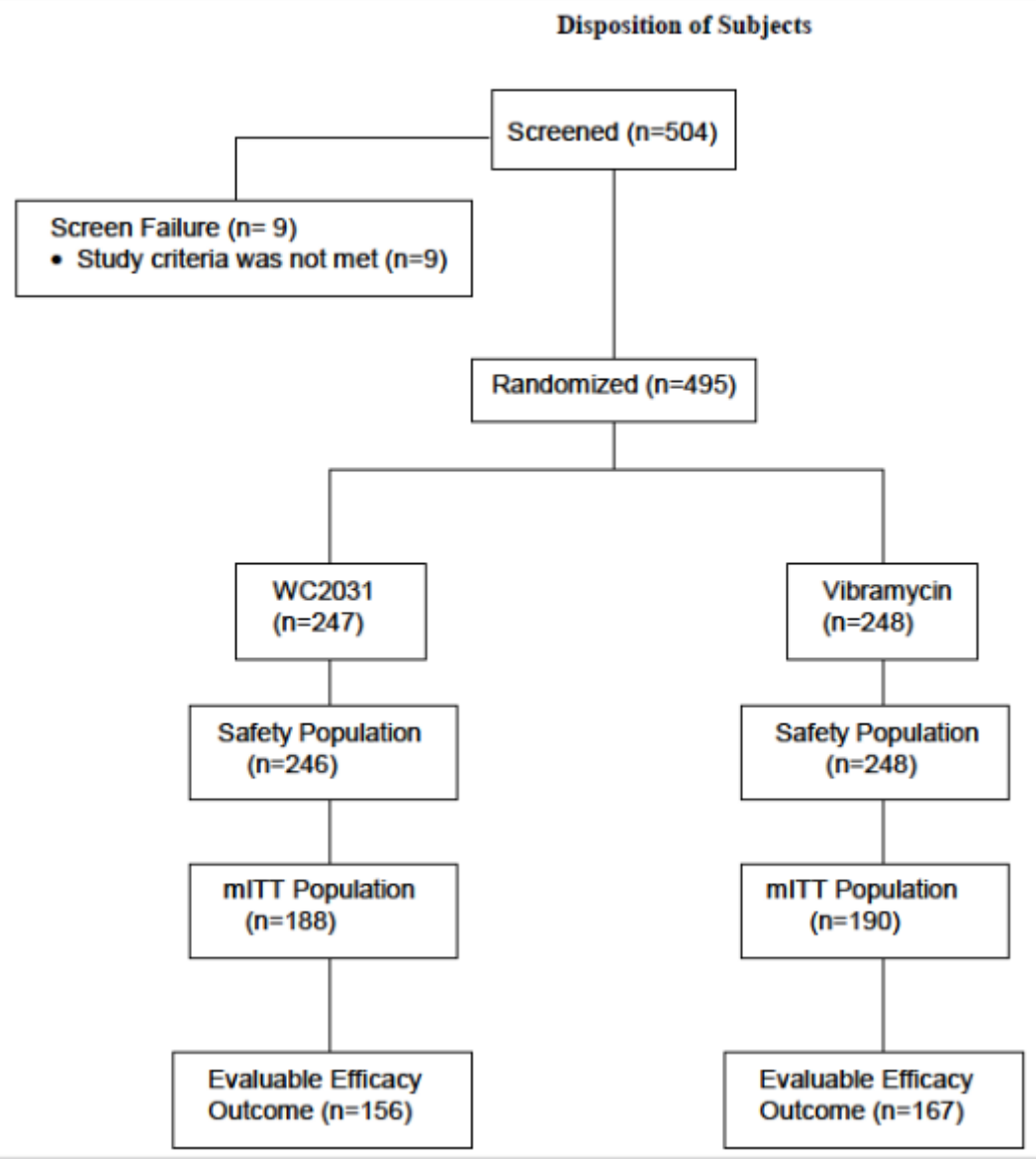

Figure 1: Disposition of Subjects

Source: S-010 Resubmission Volume 7; 8.4.1 Controlled Clinical Study PR-04809; Figure 4.

Table 2 : Summary of Subject Disposition

Disposition	WC2031	Vibramycin	Total
Subject screened			504
Screen failures – n (%) [a]			9 (1.8)
Reason for screen failure – n (%) [a]			
Study criteria not met			9 (1.8)
Subject randomized	247	248	495
Subjects in safety population – n (%) [c]	246	248	494 [b]
Subjects in mITT [h] population – n (%) [c]	188 (76.1)	190 (76.6)	378 (76.4)
Subject in clinically evaluable population – n (%) [c]	69 (27.9)	83 (33.5)	152 (30.7)
Subjects in *M. genitalium* co-infected population – n (%) [c]	15 (16.1)	12 (4.8)	27 (5.5)
Subjects in *N. gonorrhoea* co-infected population – n (%) [c]	1 (0.4)	4 (1.6)	5 (1.0)
Subjects in *N. gonorrhoea* negative population – n (%) [c]	187 (75.7)	186 (75.0)	373 (75.4)
Subjects in mITT with Evaluable Efficacy Outcome – n (%) [d]	156 (63.2)	167 (67.3)	323 (65.3)
Reason for Non-evaluability – n (%) [e]			
C. trachomatis test outside the Day 28 (-7/+14) window [f]	10 (4.0)	7 (2.8)	17 (3.4)
Non-compliant with study medication	14 (5.7)	6 (2.4)	20 (4.0)
Received exclusionary treatment that has an impact on TOC	4 (1.6)	4 (1.6)	8 (1.6)
Missing Day 28 *C. trachomatis* result [g]	17 (6.9)	10 (4.0)	27 (5.5)
Subjects with Early Termination at Any Time after Randomization – n(%) [c]	19 (7.7)	17 (6.9)	36 (7.3)
Reason for Early Termination – n (%) [c]			
Adverse Event	2 (0.8)	2 (0.8)	4 (0.8)
Investigator Discretion	0	2 (0.8)	2 (0.4)
Lost to follow-up	12 (4.9)	9 (3.6)	21 (4.2)
Withdrew consent	3 (1.2)	0	3 (0.6)
Other	2 (0.8)	4 (1.6)	6 (1.2)
Subjects Completing Study at – n (%) [c]			
Day 8	42 (17.0)	46 (18.5)	88 (17.8)
Not done	0	2 (0.8)	2 (0.4)
C. trachomatis positive at baseline	0	1 (0.4)	1 (0.2)
C. trachomatis negative at baseline	42 (17.0)	43 (17.3)	85 (17.2)
Day 28	186 (75.3)	185 (74.6)	371 (74.9)
Not done	10 (4.0)	5 (2.0)	15 (3.0)
C. trachomatis positive at baseline	171 (69.2)	178 (71.8)	349 (70.5)
C. trachomatis negative at baseline	5 (2.0)	2 (0.8)	7 (1.4)

[a] Percentages are based on all screened subjects
[b] One subjects was randomized but not dosed
[c] Percentages are based on randomized subjects. Clinically Evaluable Population is defined separately by gender based on urogenital findings. Number of subjects with early termination is defined as number of subjects randomized minus number of subjects who completed study at Day 8 or Day 28.
[d] Two subjects were also included in the analysis as treatment failures due to sensitivity to study medications
[e] Subject can have more than one reason for non-evaluability
[f] Only positive or negative C. trachomatis results are considered for this criterion
[g] Subjects with no post-baseline positive or negative C. trachomatis results are counted as having missing Day 28 results
[h] mITT – modified intent to treat

Source: S-010 Resubmission Volume 7; 8.4.1 Controlled Clinical Study PR-04809; Modified from Table 7.

6.1.3 Analysis of Primary Endpoint(s)

For the analysis of efficacy outcomes, in the initial submission the Applicant used the mITT population with evaluable efficacy outcome, i.e. the per protocol population, whereas the FDA analysis evaluated efficacy in the mITT population consisted of all randomized subjects with positive baseline *C. trachomatis* test who took at least one dose of study drug and treated all subjects with non-evaluable outcomes as failures, see Table 3 and **Table 4**.

As a reminder, the primary efficacy endpoint was the proportion of subjects with microbiological cure at the Day 28 visit, defined as a negative result for urogenital *C. trachomatis* on the GP AC2 NAAT.

Table 3: Study populations

Populations	**WC2031**	**Vibramycin**	**Total**
Randomized	247	248	495
Safety Population – n (%)	246	248	494
mITT* Population – n (%)	188 (76.1)	190 (76.6)	378 (76.4)
mITT with Evaluable Efficacy Outcome – n (%)	156 (63.2)	167 (67.3)	323 (65.3)

*modified ITT (mITT) population consisted of all randomized subjects who had a positive NAAT for *C. trachomatis* at baseline visit and took at least one dose of study drug.
Source: S-010 Resubmission Volume 7; 8.4.8 Efficacy evaluation; Table 8.

Table 4: Primary Efficacy Outcomes [a] as Originally Reported

	Applicant's Analysis [b]			**FDA Analysis [c]**		
	WC2031	Vibramycin	Difference	WC2031	Vibramycin	Difference
N	157 [d]	168 [d]		188	190	
Microbiological Cure	149 (94.9)	159 (94.6)	0.3	149 (79.3)	159 (83.7)	-4.4
95% Confidence Interval for cure rate			**-4.6, 5.1**			**-12.8, 3.9**

[a] Microbiological Cure of *C. trachomatis* at Day 28
[b] Non-evaluable outcomes are treated as missing and not included as failures
[c] Non-evaluable outcomes are treated as failures
[d] 2 non-evaluable patients, one in the WC2031 and another in Vibramycin arm are considered treatment failures because they could not take study drug due to vomiting
Source: Modified from Dr. M. Gamalo's FDA Statistical Review, 22 May 2011, Table 5 and S-010 Resubmission Volume 7, 8.4.1 Controlled Clinical Study PR-04809; Table 11.

During dispute resolution process, the FDA acknowledged that it may be too conservative to treat all subjects with non-evaluable outcomes as failures regardless of the significance of the protocol deviation that resulted in a non-evaluable status. The case report forms of these subjects were reviewed and efficacy outcomes were re-adjudicated based on the deemed significance of protocol deviation.

The results of this reassessment are presented in Table 5.

Table 5: Outcomes Assigned to 56 Subjects That Were Previously Considered Non-evaluable		
Outcomes Protocol deviation	**Treatment Arms** **Number of Subject**	
	WC2031	**Vibramycin**
Failure	**21**	**15**
Lost to follow-up	10	5
Withdrew consent	3	0
Adverse reactions, test not performed*	1	2
Completed subject, test not performed*	3	3
Intake of non-allowed medications	3	2
Other protocol deviations, not cured in window†	1	2
Other protocol deviations, test not performed	0	1
Cure	**7**	**6**
Adverse reactions, but cured	1	0
Non compliant, but cured in window	1	2
Early evaluation visit, but cured	1	1
Other protocol deviations, cured in window	4	3
Indeterminate‡	**5**	**2**
Late evaluation visit	5	2
Total	**33**	**23**

* End of study test of cure with urogenital *C. trachomatis* Nucleic Acid Amplification Test
† 21-42 day evaluation window
‡ Indeterminate – analyzed as either cure or failure

The difference between the mITT population (n=378) and the population with evaluable efficacy outcome (n=323) was 55 subjects. In addition, one more subject with non-evaluable outcome was discovered in the process of resubmission. It was determined that 36 out of 56 subjects failed, 13 were cured, and for 7 subjects the outcome was deemed undetermined. The Applicant and FDA re-analyzed the data using these outcome adjudications, Table 6.

Table 6 **: Primary Efficacy Outcomes [a] as Reanalyzed [b]**						
	Applicant's Analysis			**FDA Analysis**		
	WC2031	Vibramycin	Difference	WC2031	Vibramycin	Difference
N	188	190		188	190	
Microbiological Cure	163 (86.7)	171 (90)	-3.3	163 (86.7)	171 (90.0)	-3.3
95% Confidence Interval for Cure Rate			**-9.8, 3.2 [c]**			**-10.3, 3.7**

[a] Microbiological Cure of *C. trachomatis* at Day 28, mITT population
[b] Outcomes based on available post-baseline results as described in Table 5 of this review
[c] 95% 2-sided confidence interval using asymptotic normal approximation
Source: Modified from FDA Statistical Review, 22 May 2011, Table 12 and S-010 Resubmission Volume 7, Table 30.

According to the FDA analysis, the treatment difference between Vibramycin and WC2031 groups is -3.3% (95% CI: -10.3, 3.7) whereas Applicant's analysis demonstrates the same treatment difference of -3.3% but with 95% CI of -9.8, 3.2.

The difference in the 95% confidence intervals in the Applicant and FDA analyses are explained by the methods used to calculate them. The FDA used the Wilson's method with continuity correction whereas the Applicant used 500 imputation sets. The FDA considers its calculations to be more appropriate; the reader is referred to the statistical review for more details.

FDA performed some additional analyses. When these indeterminate outcomes are considered as failures, the microbiological cure rate in the mITT population for the WC2031 group is 82.4% versus 86.8% for the Vibramycin reference group (95% CI: -11.5%, 3.8%). When they are considered as successes, the cure rate for the WC2031 group is 85.1% versus 87.9% for the Vibramycin (CI:-9.6%, 5.0%).

Considering all evidence, the Division concluded that WC2031 may be considered non-inferior to Vibramycin for the treatment of uncomplicated urogenital *C. trachomatis* infection.

6.1.4 Analysis of Secondary Endpoints(s)

- The rates of both microbiological and clinical cure at Day 28 in subjects with clinical signs and symptoms of infection at baseline (dysuria, urethral pruritus and urethral discharge for males and examination finding of urethral discharge for females) were 80% (48/60) and 68.6% (48/70) in the WC2031 and Vibramycin groups, respectively.
- In subjects co-infected with *M*. *genitalium*, the microbiological cure rate for *M*. *genitalium* at Day 28 was 35.7% (5/14) in WC2031 group and 18.2% (2/11) in the Vibramycin group. Of note, cure rates for *C. trachomatis in M*. *genitalium co-infected subjects* were 100%, 13/13 for WC2031 and 12/12 for Vibramycin.
- Since the *N. gonorrhoeae* coinfected population had only 1 subject in the WC2031 treatment group and 4 subjects in the Vibramycin reference group, the comparison of efficacy outcomes in these subpopulations can not be determined.

7 Review of Safety

Safety Summary

There were no serious adverse events (SAEs) and no deaths reported in the phase 3 trial. The most common AE was nausea which occurred in 33 (13.4%) subjects of the WC2031 group and 51 subjects (20.6%) of the Vibramycin group. A total of 4 subjects discontinued study medication, 2 in the WC2031 group (due to headache and hypersensitivity, respectively), and 2 in the Vibramycin group (due to vomiting, and hypersensitivity plus dysphagia, respectively). No safety specific concerns related to WC2031 have been identified. A summary of adverse events (AE) is provided in Table 7. For detailed review of safety the reader is referred to Dr. Nasim Modelina's review from 06/13/2011.

Table 7: Overall Summary of Adverse Events – Safety Population

	WC2031 N=246	Vibramycin N=248
Subjects with Any AE n(%)	99 (40.2)	132 (53.2)
Number of AEs	141	219
Subjects with Any Treatment-related AE n(%)	76 (30.9)	107(43.1)
Number of treatment-related AEs	99	158
Subjects with Any Serious AE n(%)	0	0
Number of Serious AEs	0	0
Subjects with Any Severe AE n(%)	3 (1.2)	3 (1.2)
Number of Severe AEs	3	4
Subjects with Any AE Leading to Study Discontinuation -n(%)	2 (0.8)	2 (0.8)

Note: A subject with multiple occurrences of an AE is counted only once for that AE. Treatment-related includes probably related, and possibly related AEs.

Source: S-010 Resubmission Volume 7, 8.4.1 Controlled Clinical Study PR-04809; Table 35.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Division of Anti-Infective Products requested to waive pediatric studies for Doryx 200 mg tablets base. The reasons for the waiver depend on children's age and are as follows:

- Birth to less than eight years of age - as a tetracycline class antibacterial, DORYX should not be used in pediatric patients to the age of 8 years because of the effects of tetracyclines on tooth development and growth.

- Eight years of age to less than 18 years of age – Waiver for some of this age group (up to approximately 11 years of age) is justified based on studies being not feasible. There are too few instances of sexual activity in children 8-11 years of age to be able to conduct a trial of patients in this age group with sexually transmitted infections.

- For patients eight years and older diagnosed with uncomplicated urogenital *Chlamydia trachomatis* infection and treated with the adult dose of doxycycline, no significant variability as compared to adults is expected in terms of response to doxycycline 200 mg tablet taken once a day versus doxycycline 100 mg tablet taken twice a day. Thus, the Division thinks that no additional studies in the

pediatric population are needed. (Pediatric assessment for this age group should be considered completed.)

8 Postmarket Experience

Not applicable.

9 Appendices

9.2 Labeling Recommendations

The applicant has submitted proposed labeling revisions adding the new dose regimen for *C. trachomatis* infections, the description of the 200-mg tablets, and the study description in clinical studies.

The review division has recommended changes to the study description and has included the 80-mg tablet strength, added based on a manufacturing supplement being approved at the same time as this efficacy supplement.

Other changes were proposed to the labeling to make it consistent with the package insert for Pfizer's Vibramycin® tablets, since Doryx tablets were originally approved under a 505(b)(2) NDA relying on FDA findings of safety and effectiveness for the Pfizer product. These recommended changes affect the Clinical Microbiology section and the Indications and Usage sections of labeling, to match the Pfizer labeling. At the time of this review, the draft labeling was under negotiation with the applicant. Final approved labeling will be included with the approval letter for this efficacy supplement.

9.3 Advisory Committee Meeting

No advisory committee was deemed necessary for this NDA resubmission.

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/s/

DMITRI IARIKOV
03/14/2013

JOHN J ALEXANDER
03/14/2013