CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-806

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-806
Drug Name:	metronidazole vaginal gel 0.75%
Indication(s):	Treatment of bacterial vaginosis
Applicant:	TEVA Pharmaceuticals
Date(s):	Stamp date: July 20, 2004
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Biometrics Division:	Division of Biometrics III (HFD-725)
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Keywords: clinical studies, NDA review, one study application, bacterial vaginosis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of TCR-03 demonstrate that the efficacy of the Applicant's metronidazole vaginal gel 0.75% is non-inferior to MetroGel-Vaginal® in the treatment of bacterial vaginosis (BV). Even though the results of the primary endpoint, therapeutic cure at Visit 3, show statistical significance of metronidazole vaginal gel 0.75% compared to MetroGel-Vaginal®, a claim of clinical superiority is not appropriate without the confirmatory evidence of a second clinical study.

1.2 Brief Overview of Clinical Studies

One clinical study has been submitted to provide support for the use of the Applicant's formulation of metronidazole vaginal gel 0.75% for BV. Study TCR-03 was a Phase 3 randomized, double-blind, controlled trial in subjects with BV. Subjects were randomized to receive treatment with either metronidazole vaginal gel 0.75% or MetroGel-Vaginal® in a 1:1 ratio. Study medication was applied for 5 consecutive nights at bedtime. The primary efficacy endpoint was therapeutic cure at the Day 22-31 follow-up visit (Visit 3). A subject was considered a therapeutic cure if she was a clinical cure and a bacteriological cure.

1.3 Statistical Issues and Findings

A total of 579 subjects received study medication. Of these 579 patients, 229 metronidazole patients and 243 MetroGel® patients were included in the FDA-defined Modified Intent to Treat (FDA MITT) population. The Per Protocol (PP) population consisted of 155 metronidazole and 159 MetroGel® patients. In the PP analysis, the therapeutic cure rates at Visit 3 were 51.6% for the Applicant's metronidazole vaginal gel 0.75% group and 36.5% for the MetroGel® group. In the FDA MITT analysis, the therapeutic cure rates were 42.8% for the Applicant's metronidazole vaginal gel 0.75% group and 30.9% for the MetroGel® group. The 95% confidence intervals about the difference in therapeutic cure rates are (3.6, 26.6) and (2.8, 21.0), respectively. In both analyses, the Applicant's metronidazole vaginal gel 0.75% group was shown to be non-inferior to the MetroGel® group since the lower bounds of the 95% confidence intervals are greater than -20%.

2. INTRODUCTION

2.1 Overview

This submission contains the results of study TCR-03 entitled "A multi-center, double-blind, parallel group comparing the bioequivalence of TEVA Pharmaceuticals USA's generic formulation of metronidazole vaginal gel, 0.75% and Metrogel-Vaginal® metronidazole vaginal gel, 0.75% in the treatment of bacterial vaginosis." This study was designed as a

clinical bioequivalence study to show the therapeutic equivalence of the Applicant's formulation of metronidazole vaginal gel 0.75% to the reference listed drug MetroGel-Vaginal®. The study results fell outside the range of 80-120% required to demonstrate clinical bioequivalence. Therefore, Office of Generic Drugs (OGD) "refused to receive" the application as an ANDA. So the Applicant has now submitted the application as an NDA.

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 study, TCR-03. The study report and the datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\N21806\N_000\2004-10-05.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study TCR-03 was a Phase 3, randomized, double-blind, controlled trial in subjects with bacterial vaginosis (BV). The study was conducted 20 sites in the United States. Subjects were randomized to receive treatment with either TEVA Pharmaceutical USA's metronidazole vaginal gel, 0.75% or MetroGel-Vaginal® metronidazole vaginal gel 0.75% in a 1:1 ratio. Subjects applied study medication intravaginally once daily at bedtime for 5 consecutive days.

Eligible subjects included females at least 18 years of age with a clinical diagnosis of BV and Nugent score ≥ 4. A clinical diagnosis of BV was defined as having the presence of clue cells $\geq 20\%$; an off-white (milky or gray), thin, homogeneous discharge; a pH of vaginal fluid ≥ 4.7; and a positive 10% KOH whiff test. The study included 3 visits: a baseline (Day 1) visit and follow-up visits at Day 8-15 (Visit 2) and Day 22-31 (Visit 3). At each visit, the investigator performed a gynecological exam and collected specimens for the following tests: saline wet mount to check for the presence of clue cell and *Trichomonas vaginalis*; 10% KOH whiff test; vaginal fluid pH, and Gram's stain for Nugent scoring.

The primary efficacy endpoint was the proportion of subjects with therapeutic cure at Visit 3 (Day 22-31). A subject was considered a therapeutic cure if they were a clinical cure and a bacteriological cure. A subject was considered a clinical cure if all of the following were satisfied:

- The original discharge characteristic of BV returned to a normal physiological discharge
- The 10% KOH whiff test was negative
- The saline wet mount was negative for clue cells
- The vaginal fluid pH was < 4.7
- The investigator indicated that the subject did not require additional therapy for BV.

A subject was considered a bacteriological cure if she had a Nugent score < 4. An assessment of therapeutic cure was also made at Visit 2. The treatment groups were compared by constructing a confidence interval about the difference in cure rates between the test product and the reference product. The confidence interval was calculated using the normal approximation to the binomial with continuity correction.

Up to 542 subjects were to be enrolled to obtain 380 evaluable subjects, 190 in each arm. The sample size was based on an estimated therapeutic cure rate of 55% and approximately 90% power to establish therapeutic equivalence of the 2 treatments. The protocol stated that therapeutic equivalence would be concluded if the confidence interval about the difference of the therapeutic cure rates is contained within the range of -20% to 20%.

***Reviewer's Comment**: It should be noted that OGD requires 90% confidence intervals to assess the bioequivalence of 2 active compounds. To assess non-inferiority of 2 active compounds, the Division uses 95% confidence intervals. For completeness, both 90% and 95% confidence intervals will be presented in this review for the primary endpoint. However, the 95% confidence intervals will be used for drawing conclusions regarding the efficacy of the Applicant's product. It should also be noted that recent applications submitted to support the non-inferiority of BV products have used a non-inferiority margin of -15% rather than -20%.*

The protocol defined 3 analysis populations. The ITT population was defined as all subjects enrolled into the study that received at least one dose of study medication and returned for at least one visit. This population was used for the safety analyses. The MITT population was defined as all randomized subjects who received study medication, returned for at least one follow-up visit, had a negative test for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and a Gram's stain slide Nugent Score ≥4 at Visit 1. The per protocol (PP) population was defined as any subject who met all inclusion/exclusion criteria; took at least 3 consecutive days of treatment and no more than 6 days of therapy; had no study violations which could have altered the effect of, or the accurate assessment of, the applied study medication; and was assessed for efficacy at Visit 3 (within Day 22 to 31) or defined as a failure at Visit 2.

***Reviewer's Comment**: The Division does not usually consider the MITT population defined by the Applicant as an ITT-type population since this population excluded subjects based on protocol violations (not meeting inclusion/exclusion criteria). The only exception is having a Nugent score ≥4 which is used to define a subject with BV and the result is not known until after the subject has been enrolled. Therefore, an FDA MITT population was defined as all randomized subjects who received study medication and had a Nugent score ≥4. This population will be used for all analyses in place of the MITT population defined by the Applicant.*

Subjects who terminated the study prematurely due to treatment failure were carried forward as a treatment failure in both the PP and FDA MITT analyses. The Applicant applied a last-observation-carried forward (LOCF) approach for subjects who had missing data in the MITT population. The Division usually considers a worst-case scenario outcome for

subjects with missing data in the MITT analysis and this will be applied in the FDA MITT analyses.

3.1.2 Patient Demographics

A total of 579 subjects were enrolled into the study, of these, 459 subjects used study medication (220 metronidazole, 239 MetroGel®) and were included in the ITT/safety population. The FDA MITT population consisted of 229 metronidazole patients and 243 MetroGel® patients. An additional 74 metronidazole and 84 MetroGel® patients were excluded from the PP population leaving 155 metronidazole and 159 MetroGel® patients in the PP population. The most common reasons for exclusion from the PP population were test of cure visit was outside the window, subjects had a known or suspected infectious cause of vulvovaginitis other than BV, and subject started using study medication later than 2 days after Visit 1.

Table 1 summarizes the demographic characteristics of the MITT population. There were no significant differences across treatment groups. All subjects were female. Most of the subjects were black (66.1%). The mean age of the patients was 32 years with a range of 18 to 77 years.

Table 1
Demographic Characteristics (FDA MITT)

	Treatment Group	
	Metronidazole	**MetroGel®**
# Patients	229	243
Age mean (SD)	32.7 (10.7)	32.6 (10.2)
min, max	18, 71	18, 77
Race		
White	69 (30.1)	78 (32.1)
Black	153 (66.8)	159 (65.4)
Hispanic	4 (1.8)	3 (1.2)
Asian	2 (0.9)	1 (0.4)
Other	1 (0.4)	2 (0.8)

3.1.3 Efficacy Results

The results of the primary efficacy endpoint, therapeutic cure at Visit 3, are presented in Table 2 for the PP and FDA MITT populations. In the PP analysis, the therapeutic cure rates were 51.6% for the Applicant's metronidazole vaginal gel 0.75% group and 36.5% for the MetroGel® group. In the FDA MITT analysis, the therapeutic cure rates were 42.8% for the Applicant's metronidazole vaginal gel 0.75% group and 30.9% for the MetroGel® group. In both analyses, the Applicant's metronidazole vaginal gel 0.75% group was shown to be non-inferior to the MetroGel® group since the lower bounds of the 95% confidence intervals are greater than -20%. The lower bounds are also well above a non-inferiority margin of -15%.

Table 2
Therapeutic Cure Rate at Visit 3 (Day 22-31)

	metronidazole	MetroGel®	Difference 95% CI 90% CI
PP	80/155 (51.6)	58/159 (36.5)	15.1 (3.6, 26.6) (5.3, 24.8)
FDA MITT	98/229 (42.8)	75/243 (30.9)	11.9 (2.8, 21.0) (4.2, 19.6)

Reviewer's Comment *It should be noted that the results presented above for the PP analysis are slightly different than those presented in the Applicant's study report. The Applicant's analysis included an additional 6 metronidazole and 5 MetroGel® successes. These subjects did not meet the criteria necessary for clinical success (either for a discharge present or the pH was not < 4.7). However, the Applicant did not consider these symptoms to be due to BV and therefore considered the patient successfully treated for BV. The Division does not agree with this assessment so these subjects were considered failures in the Division's analyses.*

Secondary endpoints included clinical cure rates and Nugent (bacteriological) cure rates at Visit 3. These results are presented in Table 3. Non-inferiority of the Applicant's metronidazole vaginal gel 0.75% compared to MetroGel® was shown for both clinical cure and mycological cure in both analysis populations.

Table 3
Clinical Cure and Nugent Cure at Visit 3

Population	Endpoint	metronidazole	MetroGel®	Difference (95% CI)
PP	Clinical Cure	98/155 (63.2)	86/159 (54.1)	9.1 (-2.4, 20.6)
	Nugent Cure	95/155 (61.3)	77/159 (48.4)	12.9 (1.3, 24.4)
FDA MITT	Clinical Cure	120/229 (52.4)	110/243 (45.3)	7.1 (-2.3, 16.5)
	Nugent Cure	119/229 (52.0)	100/243 (41.1)	10.9 (1.5, 20.3)

3.2 Evaluation of Safety

A total of 92 (41.8%) subjects in the metronidazole group and 117 (49.0%) subjects in the MetroGel® group experienced at least one adverse event. A serious adverse event was reported in 2 subjects who received MetroGel® and the events were considered to be unrelated to the study medication. Eleven subjects (5 metronidazole and 6 MetroGel®) discontinued study drug due to a treatment-emergent adverse event. There were no deaths during the study.

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All patients are female so there is no gender analysis to perform. There was no significant difference in therapeutic cure rates by race when compared to the overall study population. The majority of the subjects in this study were less than the age of 55 (96%). Therefore differences due to age cannot be assessed using this data.

4.2 Other Special/Subgroup Populations

There are no other subgroups of interest.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

All evidence provided to support the efficacy of metronidazole vaginal gel 0.75% was from a single clinical study. The results of this study support the non-inferiority of metronidazole vaginal gel 0.75% to MetroGel®. Even though the results of the primary endpoint, therapeutic cure at Visit 3, show statistical significance of metronidazole vaginal gel 0.75% to MetroGel®, a claim of clinical superiority is not appropriate without the confirmatory evidence of a second clinical study.

5.2 Conclusions and Recommendations

The results of TCR-03 demonstrate that the efficacy of the Applicant's metronidazole vaginal gel 0.75% is non-inferior to MetroGel® in the treatment of BV.

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/s/

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