CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205-223
Drug Name:	Metronidazole vaginal gel 1.3%
Indication(s):	The treatment of bacterial vaginosis
Applicant:	Valeant Pharmaceuticals
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Keywords: clinical studies, bacterial vaginosis

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1 EXECUTIVE SUMMARY

In this submission, the Applicant is seeking the approval of metronidazole vaginal gel 1.3% for the indication of the treatment of bacterial vaginosis (BV). Metronidazole vaginal gel 1.3% will be provided as a single dose applicator with 5 g of product containing 65 mg of metronidazole. Metronidazole vaginal gel 0.75% has been approved in the United States since 1992 for the treatment of BV. The duration of treatment with metronidazole vaginal gel 0.75% is 5 days. With the approval of the higher concentration, metronidazole vaginal gel 1.3%, the Applicant is hoping to provide a single dose formulation that will be efficacious for the treatment of BV and lead to better compliance compared to the multi-dose formulation.

The primary evidence of efficacy of metronidazole vaginal gel 1.3% is based on a single Phase 3 trial: MP-1601-01. MP-1601-01 was a randomized, multicenter, double-blind study designed to evaluate the safety and efficacy of a single intravaginal dose of metronidazole vaginal gel 1.3% compared to a single intravaginal dose of vehicle gel in treating female subjects with BV. The primary efficacy endpoint was clinical cure at test of cure (TOC, Day 21 to 30) defined as return of normal physiological discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. Secondary efficacy endpoints included bacteriological cure and therapeutic cure. Bacteriological cure was defined as Nugent score < 4. Therapeutic cure was defined as a clinical and bacteriological cure. The primary analysis was a Cochran-Mantel Haenszel Chi-square test to compare the cure rates between the two treatment groups with stratification by analysis site. The difference in the cure rates between treatment groups (metronidazole vaginal gel 1.3% - vehicle gel) was also calculated along with the corresponding two-sided 95% confidence interval about the difference based on the normal approximation to the binomial.

In MP-1601-01, 651 patients were randomized to treatment and approximately 89% of the patients completed the study. The primary analysis population consisted of 250 metronidazole vaginal gel 1.3% patients and 237 vehicle gel patients. The clinical cure rates at TOC were statistically significantly higher for those patients treated with metronidazole vaginal gel 1.3% compared to vehicle gel. Clinical cure at TOC was 37.2% for metronidazole vaginal gel 1.3% and 26.6% for vehicle gel. The difference in clinical cure rates between treatment groups was 10.6% with a 95% confidence interval of (2.4%, 18.8%). Bacteriological cure at TOC was statistically significantly greater for metronidazole vaginal gel 1.3% compared to vehicle gel (18.8% vs. 8.0%, respectively). The difference in bacteriological cure rates was 10.8% with a 95% confidence interval of (4.8%, 16.7%). Therapeutic cure at TOC was statistically significantly greater for metronidazole vaginal gel 1.3% compared to vehicle gel (16.8% vs. 7.2%, respectively). The difference in therapeutic cure rates was 9.6% with a 95% confidence interval of (3.9%, 15.3%).

Supportive information comes from a small Phase 2 dose ranging study, GW05-0904. GW05-0904 was a multicenter, randomized, investigator-blind, dose ranging efficacy and safety study of metronidazole vaginal gel 1.3% (QD x 1 day, QD x 3 days, and QD x 5 days) compared with metronidazole vaginal gel 0.75% (QD x 5 days) for the treatment of BV. The primary efficacy endpoint was therapeutic cure at TOC (Day 21 to 30). Therapeutic cure required both clinical cure and bacteriological cure. Clinical cure was defined as absence of an off-white, thin,

homogeneous discharge, negative whiff test, absence of clue cells, and < 4.7 vaginal fluid pH. In addition, the subject must not have received any antimicrobial drugs during the study period and the investigator must have answered no to the question "In your opinion, does the patient require additional treatment for BV infection at this time?". Bacteriological cure was defined as Nugent Score < 4. Secondary efficacy endpoints included clinical cure at TOC and bacteriological cure at TOC. No formal statistical testing was performed to compare treatment groups. Cure rates by treatment group were used to summarize the data.

In GW05-0904, 255 patients were randomized to treatment and approximately 92% of the patients completed the study. The primary analysis population consisted of 43 metronidazole vaginal gel 1.3% x 1 day patients, 48 metronidazole vaginal gel 1.3% x 3 day patients, 49 metronidazole vaginal gel 1.3% x 5 day patients, and 49 metronidazole vaginal gel 0.75% x 5 day patients. Therapeutic cure rates at TOC were numerically higher for all metronidazole vaginal gel 1.3% groups compared to metronidazole vaginal gel 0.75%. For the secondary endpoint of clinical cure at TOC, it was also demonstrated that response rates were numerically higher for all metronidazole vaginal gel 1.3% groups compared to metronidazole vaginal gel 0.75%. Bacteriological cure rates at TOC were numerically similar (metronidazole vaginal gel 1.3% x 1 day) or numerically higher (metronidazole vaginal gel 1.3% x 3 days or x 5 days) as compared to the metronidazole vaginal gel 0.75% x 5 day group.

Based on the results of the pivotal trial, the trial met its stated objective in that the clinical cure rate was significantly higher with treatment with metronidazole vaginal gel 1.3% compared to vehicle gel. Similar results were shown for the secondary endpoints of bacteriological and therapeutic cure. Supportive information was provided by the small Phase 2 dose response trial as well as the safety and efficacy studies available for MetroGel Vaginal 0.75% which were reviewed for the approval of NDA 20-208. Therefore, there is adequate evidence of efficacy to support the indication of the treatment of BV for metronidazole vaginal gel 1.3%.

2 INTRODUCTION

2.1 Overview

This is an NDA submission for metronidazole vaginal gel 1.3%. The indication being sought by the Applicant is the treatment of bacterial vaginosis (BV). Metronidazole vaginal gel 0.75% has been approved for the treatment of bacterial vaginosis since 1992. The duration of treatment with metronidazole vaginal gel 0.75% is 5 days whereas the proposed higher concentration formulation will be given as a single dose.

The development program for metronidazole vaginal gel 1.3% consisted of a single Phase 1 pharmacokinetic study in healthy females, a Phase 2 dose ranging study, and a single Phase 3 trial. Primary support of the efficacy of metronidazole vaginal gel 1.3% is based on the Phase 3 trial, MP-1601-01. MP-1601-01was a randomized, multicenter, double- blind study designed to evaluate the safety and efficacy of a single intravaginal dose of metronidazole vaginal gel 1.3% compared to a single intravaginal dose of vehicle gel in treating female subjects with BV. Supportive efficacy data comes from the Phase 2 dose ranging study- GW05-0904. GW05-0904

evaluated the safety and efficacy of metronidazole vaginal gel 1.3% administered once daily for 1, 3, or 5 days compared with MetroGel-Vaginal 0.75% administered once daily for 5 days. Additional supportive data is provided by the ten clinical studies (4 Phase 1, 2 Phase 2, and 4 Phase 3 studies) that were the basis of approval for MetroGel-Vaginal (metronidazole vaginal gel 0.75%), NDA 20-208. The focus of this review will be the pivotal Phase 3 efficacy trial although the Phase 2 trial will be briefly summarized.

An End of Phase 2 meeting was held with the Medical Division on August 25, 2010 to discuss the results of the Phase 2 trial and the proposed Phase 3 clinical program. At this meeting, the Medical Division agreed that the safety and efficacy studies available for the treatment of BV with MetroGel-Vaginal 0.75% could be used as supportive information and therefore only a single Phase 3 trial with metronidazole vaginal gel 1.3% would be needed. Since the Applicant is the owner of the MetroGel-Vaginal 0.75% data, this information could be cross referenced rather than resubmitted in the NDA for metronidazole vaginal gel 1.3%.

The Phase 3 protocol was submitted as a Special Protocol Assessment (SPA). The SPA received a non-agreement letter primarily due to the primary endpoint. In the SPA non-agreement letter, the Medical Division indicated that the current recommendation for the primary endpoint in BV trials was clinical cure rather than therapeutic cure (clinical plus Nugent cure). Clinical cure was to be defined as return of normal physiological discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. Nugent score was to still be assessed as a secondary endpoint. The Medical Division did concur with a placebo-controlled superiority study design proposed for the Phase 3 study in the SPA non-agreement letter. The Applicant revised the protocol to change the primary endpoint as stated in the SPA non-agreement letter but did not resubmit the protocol as an SPA.

Table 1
Listing of Studies Included in Review

Protocol	**Phase and Design**	**Dosing Regimen/ Duration of Treatment**	**# of Subjects per Arm**	**Study Population**
MP-1601-01	Phase 3 multi-center, randomized, double-blind, vehicle-controlled	Single dose metronidazole vaginal gel 1.3% or vehicle gel for 1 day	325 metronidazole vaginal gel 1.3% 326 vehicle gel	Female patients diagnosed with BV
GW05-0904	Phase 2 multi-center, randomized, investigator blind, dose ranging	Metronidazole vaginal gel 1.3% once daily for 1, 3, or 5 days or MetroGel-Vaginal 0.75% for 5 days	65 metronidazole vaginal gel 1.3% x 1 day 60 metronidazole vaginal gel 1.3% x 3 days 64 metronidazole vaginal gel 1.3% x 5 days 66 MetroGel-Vaginal 0.75% x 5 days	Female patients diagnosed with BV

2.2 Data Sources

The data analyzed in this review comes from the Phase 2 and Phase 3 trials submitted as the evidence to support the efficacy of metronidazole vaginal gel 1.3%. The final MP-1601-01 study report, the GW05-0904 study report, and datasets for the two studies provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\cdsesub1\EVSPROD\NDA204251\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets submitted were of acceptable quality. Minimal programming was necessary to reproduce the results presented by the Applicant.

Reviewer's Comment: *Unless otherwise indicated, tables presented in this review are based on analyses conducted by this reviewer using the analysis datasets submitted by the Applicant and confirm the results of those presented by the Applicant in the MP-1601-01 and GW05-0904 Study Reports.*

3.2 Evaluation of Efficacy

3.2.1 Study MP-1601-01

3.2.1.1 Study Design and Endpoints

MP-1601-01 was a Phase 3, multicenter, randomized, double-blind, vehicle-controlled study designed to evaluate the safety and efficacy of a single dose of metronidazole vaginal gel 1.3% compared to a single dose of vehicle gel for the treatment of BV. The study was conducted at 37 investigational centers in the United States. Patients were evaluated at 3 time points: screening/baseline, Day 7 post-treatment, and Day 21 test of cure (TOC). Patient eligibility was determined at the screening/baseline visit. Females aged 18 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects were to have a Nugent score > 4. However, the results of the Gram stain for the Nugent score were not known until after randomization. Additionally, subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or active *H. simplex)* were to be excluded. Eligible subjects were randomized in a 1:1 ratio to receive treatment with either metronidazole vaginal gel 1.3% or vehicle gel. Treatment was to be applied intravaginally at bedtime on Day 0. Subjects returned to the clinic on Day 7 (-0/+2 days) to assess initial therapeutic response. The TOC visit was conducted at Day 21 (-0/+9 days). At all visits, a gynecological exam was conducted and vaginal fluid specimens were collected.

The primary objective of the study was to demonstrate the safety and efficacy of a single dose of metronidazole vaginal gel 1.3% compared to a single dose of vehicle gel. The primary efficacy endpoint was clinical cure at TOC defined as return of normal physiological discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. Secondary efficacy endpoints included vaginal pH, Nugent score, investigator overall assessment, subject diary questionnaire, treatment satisfaction questionnaire for medication, and leakage assessment. Bacteriological cure was defined as Nugent score < 4. Therapeutic cure was defined as a clinical and bacteriological cure.

Reviewer's Comment: *This review will focus on the endpoints of clinical cure, bacteriological cure, and therapeutic cure.*

There was one amendment made to the protocol during the conduct of the study. On the original case report form (CRF), investigators were requested to assess vaginal discharge at the Day 7 and Day 21 visits as "Present" or "Absent". Some investigators interpreted "Present" as any discharge whether abnormal or normal thus, making it difficult to accurately assess clinical response which allowed for discharge as long as it was considered to be physiologically normal. After a number of subjects were assessed with this version of the CRF, the CRF was modified to ask the question "Has the original discharge characteristic of bacterial vaginosis returned to a normal physiological discharge?" with a "Yes" or "No" response. The change in the CRF was made to ensure a more accurate assessment of clinical response with respect to discharge could be made. As a result of this change in the collection of information regarding discharge, a primary modified intent to treat population (PMITT) was added to exclude subjects assessed using the original version of the CRF and defined as the primary analysis population. Additionally, the total sample size of the study was revised to ensure sufficient numbers of subjects in the PMITT population.

3.2.1.2 Statistical Methodologies

The primary analysis of clinical cure was based on a Cochran-Mantel-Haenszel chi-square test to compare the clinical cure rates between the 2 treatment groups with stratification by analysis site. For investigative sites with less than 8 evaluable subjects per treatment arm at a site, pooling of sites was done to form analysis sites. Sites were pooled by taking the site with the smallest enrollment and combining it with the site with the largest enrollment that did not have the minimum requirement. This process continued until the minimum criterion was met. Twenty-one analysis sites were formed from the 37 investigative sites. The difference in cure rates between the two treatment groups was also calculated and the two sided 95% confidence interval about the difference was estimated based on the normal approximation to the binomial distribution. Missing data for assessing clinical response were imputed as a failure.

The following secondary endpoints were tested in a sequential hierarchical manner:

1. Proportion of subjects with bacteriological cure at TOC
2. Proportion of subjects with therapeutic cure at TOC
3. Proportion of subjects with bacteriological cure at Day 7
4. Proportion of subjects with clinical cure at Day 7
5. Time to resolution of symptoms through Day 7.

Statistical significance was based on a two-sided type I error rate of 5%. If significance was not shown for a given secondary endpoint, then no further testing of the remaining secondary endpoints was to be conducted. The first 4 secondary endpoints were analyzed using a Cochran-Mantel-Haenszel chi-square test stratified by analysis site. Time to resolution of symptoms was analyzed using Kaplan-Meier method and treatment comparisons were made using the log rank test.

Five data sets were used in analyses. The modified intent-to-treat (MITT) population included all randomized patents that had a Gram stain Nugent score ≥4 at baseline and a negative test for *C. trachomatis* and *N. gonorrhoeae* at baseline. The primary modified intent to treat (PMITT) population is a subset of all MITT subjects who were enrolled at a time such that their Day 21 evaluation would be conducted with the revised CRF using the criterion "Has the original discharge characteristic of BV returned to a normal physiological discharge?" i.e. excluded those evaluated with the original CRF (see further discussion in Section 5.1). The PMITT population is the primary efficacy analysis population. The per-protocol (PP) population is a subset of the PMITT population who met the following: satisfied all inclusion and exclusion criteria and had no protocol violations; started study medication on the day of or within 2 days of randomization; were compliant with study medication; had no antimicrobial drug use (other than allowed by protocol) during study period; had no additional intravaginal products during the duration of the study; had a TOC Gram stain Nugent score result obtained between study Days 21 and 30. The PP population was used as a supportive analysis population for the primary efficacy endpoint. The Day 7 Analysis population is a subset of the PMITT population who were to have their Day 7 vaginal discharge evaluated with the revised CRF using the criterion: "Has the original discharge characteristic of BV returned to a normal physiological discharge?". Analyses of the secondary endpoints at Day 7 were based on the Day 7 Analysis population. The Safety population included all randomized subjects who applied study medication. Subjects were analyzed as randomized for each of the efficacy populations and as treated for the Safety population.

Sample size was based on assuming a 2-sided alpha of 5%, at least 90% power, a clinical cure rate of 38% in the metronidazole vaginal gel 1.3% group, and a clinical cure rate of 22% in the vehicle gel group. Thus, a sample size of 183 per treatment group (366 total) was needed. It was assumed that approximately 40% would be ineligible for the MITT population. Therefore, 570 subjects were to be randomized. After the amendment which made the PMITT population the primary efficacy analysis population, the total number of subjects randomized was increased to 650 subjects to ensure that 366 subjects would be evaluable in the PMITT population.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 651 patients were randomized into the study: 325 to the metronidazole vaginal gel 1.3% group and 326 to the vehicle gel group. Approximately 89% of the randomized patients completed the study. The most common reasons for discontinuation from the study were subject's request (not due to AE), lost to follow-up, or positive for other vulvovaginal infections. Reasons for discontinuation from the study are reported in Table 2.

Table 2
MP-1601-01
Patient Disposition

	Metronidazole Gel 1.3%	Vehicle Gel
Randomized	325	326
Completed Study	293 (90.2)	288 (88.3)
Discontinued Study	32 (9.8)	38 (11.7)
Adverse Event	0	0
Investigator's request	0	2
Subject's request (not due to AE)	7	12
Lost to Follow-up	10	9
Positive for *N. gonorrhoeae* or *C. trachomatis*	8	10
Other	7	5

All subjects received the treatment to which they were randomized. The Safety Population is comprised of 637 patients: 4 subjects randomized to receive metronidazole vaginal gel 1.3% and 10 randomized to receive placebo gel did not apply study medication and were excluded. Seventy-four subjects were excluded from the MITT population (33 metronidazole vaginal gel 1.3% and 41 vehicle gel). Most were excluded for not having a baseline Nugent score ≥4 (24 metronidazole vaginal gel 1.3% and 28 vehicle gel). The remaining subjects were excluded from the MITT because they were positive at baseline for either *N. gonorrhoeae* or *C. trachomatis*. A total of 164 subjects were excluded from the PMITT population, this includes an additional 90 subjects (42 metronidazole vaginal gel 1.3% and 48 vehicle gel) since they were enrolled at a time such that they were not evaluated at Day 21 for vaginal discharge with the revised CRF using the criterion "Has the original discharge characteristic of BV returned to a normal physiological discharge?" but with the original CRF instead. There were 8 subjects (5 metronidazole vaginal gel 1.3% and 3 vehicle gel) included in the PMITT population even though they were enrolled prior to the amendment of the case report form because there was sufficient information recorded in the source documents to allow the investigator to determine a response to the question. An additional 69 patients (36 metronidazole vaginal gel 1.3% and 33 vehicle gel) were excluded from the PP population due to protocol violations, primarily due to not having a Gram Stain Nugent Score assessed between Day 21 and 30.

Table 3
MP-1601-01
Analysis Populations

	Metronidazole Gel 1.3%	Vehicle Gel
Randomized	325	326
Safety Population	321	316
MITT Population	292	285
PMITT Population	250	237
PP Population	214	204

Reviewer's Comment: *There is some concern regarding the inclusion of the additional 8 subjects in the PMITT. These subjects were not evaluated at Day 21 with the revised CRF (i.e. enrolled prior to the revision of the CRF) which was the requirement for inclusion in the PMITT population. The subjects were included by the Sponsor because there was other source documentation that would allow for the assessment of a response to the revised discharge question. See further discussion in Section 5.1*

Table 4 summarizes the demographic and baseline characteristics of the PMITT population. There were no significant differences between treatment groups. Overall, 60% of the study population was black and 37% was white. The mean age of the patients was 33 years. The median baseline Nugent score was 8. Vulvovaginal itching, irritation, and inflammation were absent in the majority of subjects (69%, 63%, 65%, respectively) and those symptoms that were reported were primarily mild in nature. Demographic and baseline characteristics of the MITT and PP populations were comparable to the PMITT population. With the exception of baseline Nugent Score, subjects in the Safety population were comparable to the PMITT population. This is due to the fact that by definition of the PMITT population subjects with a Nugent Score less than 4 were excluded.

Table 4
MP-1601-01
Demographic and Baseline Characteristics (PMITT)

	Treatment Group	
	Metronidazole Gel 1.3%	**Vehicle Gel**
# Patients	250	237
Age mean (SD)	32.2 (9.1)	34.6 (9.7)
Min, max	18, 63	18, 67
Race		
White	94 (37.6)	86 (36.3)
Black	149 (59.6)	146 (61.6)
Asian	2 (0.8)	1 (0.4)
Other	5 (2.0)	4 (1.7)
Nugent Score mean (SD)	8.5 (1.5)	8.4 (1.5)
median	8	8
Min, max	4, 10	4, 10
Vulvovaginal Itching		
Present	76 (30.4)	76 (32.1)
Absent	174 (69.6)	161 (67.9)
Vulvovaginal Irritation		
Present	88 (35.2)	94 (39.7)
Absent	162 (64.8)	143 (60.3)
Vulvovaginal Inflammation		
Present	79 (31.6)	92 (38.8)
Absent	171 (68.4)	145 (61.2)

3.2.1.4 Results and Conclusions

Clinical Cure at TOC (Day 21-30) is presented in Table 5. For the PMITT population, significantly more metronidazole vaginal gel 1.3% subjects experienced clinical cure at TOC

compared to vehicle gel subjects (37.2% vs. 26.6%, CMH p=0.010). The results for the PP and MITT populations are supportive of those seen for the PMITT.

Table 5
MP-1601-01
Clinical Cure at TOC (Day 21-30)

	Metronidazole Gel 1.3%	Vehicle Gel	p-value	Difference (95% CI)
PMITT	93/250 (37.2)	63/237 (26.6)	0.010	10.6 (2.4, 18.8)
PP	87/214 (40.7)	61/204 (29.9)	0.007	10.8 (1.7, 19.9)
MITT	108/292 (37.0)	76/285 (26.7)	0.007	10.3 (2.8, 17.9)

Table 6 summarizes clinical response at TOC for the PMITT population including the reason for clinical failure. Most subjects were failures because none of the three criteria needed for clinical cure were resolved although slightly more vehicle gel subjects compared to metronidazole vaginal gel 1.3% were failures due to this reason. In both treatment groups, approximately 12% of subjects were failures because the TOC assessment was not done. However, 14 subjects (5 metronidazole vaginal gel 1.3% and 9 vehicle gel) had early termination visits due to clinical failure and 8 subjects (5 metronidazole vaginal gel 1.3% and 3 vehicle gel) were imputed as clinical failure based on other source documentation indicating an abnormal discharge was present.

Table 6
MP-1601-01
Clinical Response at TOC (PMITT)

	Metronidazole Gel 1.3% (n=250)	Vehicle Gel (n=237)
Clinical Cure	93 (37.2)	63 (26.2)
Clinical Failure	157 (62.8)	174 (73.4)
All 3 criteria not met	92 (36.8)	119 (50.2)
2 of 3 criteria not met	19 (7.6)	20 (8.4)
1 of 3 criteria not met	16 (6.4)	6 (2.5)
Not Done	30 (6.4)	29 (12.2)
Early Termination (failure)	5	9
Other Source Documentation available	5	3
Missing	20	17

Table 7 summarizes the results for the individual components of clinical cure at TOC for the PMITT population.

Table 7
MP-1601-01
Individual Components of Clinical Cure at TOC (PMITT)

	Metronidazole Gel 1.3% (n=250)	**Vehicle Gel** (n=237)
Discharge returned to Normal		
Yes	108 (43.2)	78 (32.9)
No	112 (44.8)	130 (54.9)
Not Done	30 (12.0)	29 (12.2)
Clue Cells		
< 20%	108 (43.2)	72 (30.4)
≥ 20%	112 (44.8)	136 (57.4)
Not Done	30 (12.0)	29 (12.2)
Whiff Test		
Negative	114 (45.6)	71 (30.0)
Positive	106 (42.4)	137 (57.8)
Not Done	30 (12.0)	29 (12.2)

The results for bacteriological cure at TOC, therapeutic cure at TOC, bacteriological cure at Day 7, and clinical cure at Day 7 for the PMITT (or Day 7 analysis population) and MITT populations are summarized in Table 8. For each of the secondary endpoints, a statistically significant greater proportion of subjects achieved cure (bacteriological, therapeutic, or clinical depending on endpoint) in the metronidazole vaginal gel 1.3% group as compared to the vehicle gel group. The results for the PMITT (or Day 7 analysis population) and the MITT populations were consistent.

Table 8
MP-1601-01
Analysis of Secondary Endpoints

	Metronidazole Gel 1.3%	**Vehicle Gel**	**p-value**	**Difference (95% CI)**
Bacteriological Cure at TOC- PMITT	47/250 (18.8)	19/237 (8.0)	<0.001	10.8 (4.8, 16.7)
Bacteriological Cure at TOC- MITT	57/292 (19.5)	22/285 (7.7)	<0.001	11.8 (6.3, 17.3)
Therapeutic Cure at TOC- PMITT	42/250 (16.8)	17/237 (7.2)	0.001	9.6 (3.9, 15.3)
Therapeutic Cure at TOC - MITT	49/292 (16.8)	18/285 (6.3)	<0.001	10.5 (5.3, 15.6)
Bacteriological Cure at Day 7- Day 7 analysis population	66/202 (32.7)	13/205 (6.3)	<0.001	26.3 (19.1, 33.6)
Bacteriological Cure at Day 7- MITT	99/292 (33.9)	18/285 (6.3)	<0.001	27.6 (21.5, 33.7)
Clinical Cure at Day 7- Day 7 analysis population	93/202 (46.0)	41/205 (20.0)	<0.001	26.0 (17.3, 34.8)
Clinical Cure at Day 7- MITT	120/292 (41.1)	57 /285 (20.0)	<0.001	21.1 (13.8, 28.4)

3.2.2 Study GW05-0904

3.2.2.1 Study Design and Endpoints

GW05-0904 was a Phase 2, multicenter, randomized, investigator-blind, dose ranging efficacy and safety study of metronidazole vaginal gel 1.3% (QD x 1 day, QD x 3 days, and QD x 5 days) compared with metronidazole vaginal gel 0.75% (QD x 5 days) for the treatment of BV. The study was conducted at 20 investigational centers in the United States. Patients were evaluated at 3 time points: screening/baseline, a post-treatment phone call, and TOC visit. Patient eligibility was determined at the screening/baseline visit. Females aged 18 years of age and older with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. Subjects were to have a Nugent score > 4. However, the results of the Gram stain for the Nugent score were not known until after randomization. Additionally, subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis, C. trachomatis, N. gonorrhoeae,* or active *H. simplex)* were to be excluded. Eligible subjects were randomized in a 1:1:1:1 ratio to receive treatment with either metronidazole vaginal gel 1.3% (single dose for 1 day, 3 days, or 5 days) or with metronidazole vaginal gel 0.75% (single dose for 5 days). Treatment was to be applied intravaginally at bedtime. Subjects were contacted by telephone between Days 8 and 10 to assess initial therapeutic response. Subjects who were considered to have inadequate clinical response were to return to the clinic as soon as possible for a full evaluation. The TOC visit was conducted between Days 21 and 30. At all clinic visits, a gynecological exam was conducted and vaginal fluid specimens were collected.

The primary objective of the study was to evaluate the safety and efficacy of metronidazole vaginal gel 1.3% administered once daily for 1, 3, or 5 days compared metronidazole vaginal gel 0.75% once daily for 5 days. The primary efficacy endpoint was therapeutic cure at TOC. Therapeutic cure required both clinical cure and bacteriological cure. Clinical cure was defined as absence of an off-white, thin, homogeneous discharge, negative whiff test, absence of clue cells, and < 4.7 vaginal fluid pH. In addition, the subject must not have received any antimicrobial drugs during the study period and the investigator must have answered no to the question "In your opinion, does the patient require additional treatment for BV infection at this time?". Bacteriological cure was defined as Nugent Score < 4. Secondary efficacy endpoints were clinical cure at TOC, bacteriological cure at TOC, time to resolution of symptoms, return of symptoms, pelvic examination results including itching, irritation, and inflammation at TOC, treatment satisfaction questionnaire, and leakage assessment.

Reviewer's Comment: *This review will focus on the endpoints of therapeutic cure, clinical cure, and bacteriological cure.*

3.2.2.2 Statistical Methodologies

No formal statistical testing was performed to compare treatment groups. Final selection of the treatment regimen to be carried forward into the Phase 3 trial was based on cure rates, consistency of results, safety, and convenience information. For cure rates, the data was

summarized by treatment group along with exact 95% confidence intervals about the proportion cured. Missing data due to treatment failure or early discontinuation were imputed as a failure.

Four data sets were used in analyses. The intent-to-treat (ITT) population included all randomized subjects. This population was used to summarize subject disposition, demographic and baseline characteristics, medical history, and prior/concomitant medications. The MITT population included all randomized patents who received study medication kit, returned for at least 1 post-baseline assessment, had a Gram stain Nugent score ≥4 at baseline and a negative test for *C. trachomatis* and *N. gonorrhoeae* at baseline. The MITT population was used for supportive efficacy analyses. The PP population is a subset of the MITT population who met the following: satisfied all inclusion and exclusion criteria and had no protocol violations; started study medication on the day of or within 2 days of randomization; were compliant with study medication; had no antimicrobial drug use (other than allowed by protocol) during study period; had no additional intravaginal products during the duration of the study; had a TOC Gram stain Nugent score result obtained between study Days 20 and 31. The PP population was the primary efficacy analysis population. The Safety population included all randomized subjects who applied study medication. Subjects were analyzed as randomized for each of the efficacy populations and as treated for the Safety population.

Reviewer's Comment: *Typically, exclusions from the MITT population for reasons related to post-baseline factors would not be acceptable. However, for this study, no subjects were excluded from the MITT population for not receiving study medication kit or not returning for at least 1 post-baseline visit.*

Sample size was based on providing a precise estimate of therapeutic cure. Assuming a therapeutic cure rate of 51.6%, a sample of 45 subjects would provide an estimate of therapeutic cure with a 95% confidence interval width of 15%. To allow for a 25% ineligibility assessment, a sample size of 60 subjects per group (240 total) was planned for randomization.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Overall 255 patients were randomized into the study: 65 to the metronidazole vaginal gel 1.3% x 1 day group, 60 to the metronidazole vaginal gel 1.3% x 3 day group, 64 to the metronidazole vaginal gel 1.3% x 5 day group, and 66 to the metronidazole vaginal gel 0.75% x 5 day group. Approximately 92% of the randomized patients completed the study. The most common reasons for discontinuation were lost to follow-up, positive for other vulvovaginal infections, or other reason not related to an adverse event. Reasons for discontinuation are reported in Table 9.

Table 9
GW-05-0904
Patient Disposition

	1.3% x 1 day	1.3% x 3 days	1.3% x 5 days	0.75% x 5 days
Randomized	65	60	64	66
Completed Study	57 (87.7)	55 (91.7)	63 (98.4)	59 (89.4)
Discontinued Study	8 (12.3)	5 (8.3)	1 (1.6)	7 (10.6)
Investigator's request	1	0	0	0
Subject's request (not due to AE)	0	1	0	0
Non-compliance	0	0	0	1
Lost to Follow-up	4	3	1	1
Positive for *N. gonorrhoeae* or *C. trachomatis*	1	0	0	4
Other	2	1	0	1

All subjects received the treatment to which they were randomized and were included in the ITT population. The Safety Population is comprised all patients randomized with the exception of 1 patient randomized to the metronidazole vaginal gel 0.75% x 5 days group who did not apply study medication even though they received the study medication kit. Twenty-seven subjects were excluded from the MITT population (6 metronidazole vaginal gel 1.3% x 1 day, 6 metronidazole vaginal gel 1.3% x 3 days, 8 metronidazole vaginal gel 1.3% x 5 days, and 7 metronidazole vaginal gel 0.75% x 5 days). Most were excluded for not having a baseline Nugent score ≥4 (5 metronidazole vaginal gel 1.3% x 1 day, 6 metronidazole vaginal gel 1.3% x 3 days, 8 metronidazole vaginal gel 1.3% x 5 days, and 4 metronidazole vaginal gel 0.75% x 5 days). The remaining subjects were excluded from the MITT because they were positive at baseline for either *N. gonorrhoeae* or *C. trachomatis.* Thirty-nine patients (16 metronidazole vaginal gel 1.3% x 1 day, 6 metronidazole vaginal gel 1.3% x 3 days, 7 metronidazole vaginal gel 1.3% x 5 days, and 10 metronidazole vaginal gel 0.75% x 5 days) were further excluded from the PP population due to protocol violations, primarily due to not having a Gram Stain Nugent Score assessed between Day 21 and 30.

Table 10
GW-05-0904
Analysis Populations

	1.3% x 1 day	1.3% x 3 days	1.3% x 5 days	0.75% x 5 days
ITT population	65	60	64	66
Safety Population	65	60	64	65
MITT Population	59	54	56	59
PP Population	43	48	49	49

Table 11 summarizes the demographic and baseline characteristics of the ITT population. There were no significant differences between treatment groups. Overall, 52% of the study population was black and 48% was white. The mean age of the patients was 35 years.

Table 11
GW-05-0904
Demographic and Baseline Characteristics (ITT)

	1.3% x 1 day	1.3% x 3 days	1.3% x 5 days	0.75% x 5 days
# Patients	65	60	64	66
Age mean (SD)	35.0 (10.1)	33.0 (9.0)	37.4 (10.9)	35.0 (9.3)
Min, max	19, 66	18, 59	21, 67	19, 60
Race				
White	33 (50.8)	27 (45.0)	28 (43.8)	33 (50.0)
Black	32 (49.2)	32 (53.3)	36 (56.3)	32 (48.5)
Other	0	1 (1.7)	0	1 (1.5)

3.2.2.4 Results and Conclusions

Table 12 summarizes the therapeutic, clinical, and bacteriological cure rates at TOC for the per protocol and MITT populations. Therapeutic cure rates were numerically higher for all metronidazole vaginal gel 1.3% groups as compared to the metronidazole vaginal gel 0.75% group. Clinical cure rates were also numerically higher for all metronidazole vaginal gel 1.3% groups as compared to the metronidazole vaginal gel 0.75% group. As compared to the metronidazole vaginal gel 0.75% group, bacteriological cure rates were numerically similar (metronidazole vaginal gel 1.3% x 1 day) or numerically higher (metronidazole vaginal gel 1.3% x 3 days or x 5 days). While tests of statistical significance were not performed per the protocol, no treatment comparisons were statistically significant in exploratory analysis conducted. Based on these results, the Applicant concluded that when metronidazole vaginal gel 1.3% was applied daily for 1, 3, or 5 days, the medication provided comparable or numerically greater clinical/microbiologically-assessed cure rates than the metronidazole vaginal gel 0.75% formulation given for 5 days. As the single dose of metronidazole vaginal gel 1.3% had the highest patient acceptability, the Applicant chose to take this dose forward for study in the Phase 3 trial.

Table 12
GW-05-0904
Summary of Cure Rates at Test of Cure

		1.3% x 1 day	1.3% x 3 days	1.3% x 5 days	0.75% x 5 days
PP	Therapeutic	13/43 (30.2)	12/48 (25.0)	16/49 (32.7)	10/49 (20.4)
	Clinical	16/43 (37.2)	17/48 (35.4)	22/49 (44.9)	14/49 (28.6)
	Bacteriological	13/43 (30.2)	17/48 (35.4)	23/49 (46.9)	15/49 (30.6)
MITT	Therapeutic	15/59 (25.4)	12/54 (22.2)	17/56 (30.4)	12/59 (20.3)
	Clinical	18/59 (30.5)	17/54 (31.5)	23/56 (41.1)	17/59 (28.8)
	Bacteriological	18/59 (30.5)	18/54 (33.3)	26/56 (46.4)	18/59 (30.5)

3.3 Evaluation of Safety

For Study MP-1601-01, the Safety population consisted of 321 metronidazole vaginal gel 1.3% subjects and 316 vehicle gel subjects. Overall, 19.0% (61/321) metronidazole vaginal gel 1.3% treated subjects and 16.1% (51/316) vehicle gel treated subjects experienced a treatment

emergent adverse event (TEAE). The TEAEs were primarily mild in intensity and have been previously reported for marketed metronidazole products. The most commonly reported adverse event was vulvovaginal candidiasis (VVC) which occurred in 11 (3.4%) metronidazole vaginal gel 1.3% treated subjects and 8 (2.5%) vehicle gel treated subjects. The occurrence of VVC following treatment for BV is not uncommon. There were no serious TEAEs, discontinuations due to adverse events, or deaths during the study.

For Study GW-05-0904, the Safety population consisted of 65 subjects in the metronidazole vaginal gel 1.3% x 1 day group, 60 subjects in the metronidazole vaginal gel 1.3% x 3 day group, 64 subjects in the metronidazole vaginal gel 1.3% x 5 day group, and 65 subjects in the metronidazole vaginal gel 0.75% x 5 day group. Overall, 35.4% metronidazole vaginal gel 1.3% x 1 day group, 31.7% metronidazole vaginal gel 1.3% x 3 day group, 34.4% metronidazole vaginal gel 1.3% x 5 day group, and 43.1% metronidazole vaginal gel 0.75% x 5 day group subjects experienced a TEAE. The most commonly reported TEAEs were VVC and headache. VVC occurred in 8 (12.3%) metronidazole vaginal gel 1.3% x 1 day subjects, 8 (13.3%) metronidazole vaginal gel 1.3% x 3 day subjects, no metronidazole vaginal gel 1.3% x 5 day subjects, and 9 (13.8%) metronidazole vaginal gel 0.75% x 5 day subjects. Headache occurred in 3 (4.6%) metronidazole vaginal gel 1.3% x 1 day subjects, 5 (8.3%) metronidazole vaginal gel 1.3% x 3 day subjects, 7 (6.3%) metronidazole vaginal gel 1.3% x 5 day subjects, and 9 (13.8%) metronidazole vaginal gel 0.75% x 5 day subjects. The majority of the TEAEs were mild to moderate in intensity. One subject in the metronidazole vaginal gel 1.3% x 1 day group reported 2 severe adverse events: vaginal burning sensation and vulval edema. There was a single serious TEAE of hypoglycemia reported during the study by a subject in the metronidazole vaginal gel 1.3% x 1 day group. There were no discontinuations due to adverse events or deaths during the study.

A lower incidence of VVC was observed in Study MP-1601-01 as compared to Study GW-05-0904. The Applicant states that some of this difference is due to the reporting of vulvovaginal candidiasis and vulvovaginal mycotic infections as separate preferred terms in Study MP-1601-01. If these two terms were combined, the incidence would still be lower in Study MP-1601-01 (5.6% metronidazole vaginal gel 1.3% and 3.2% vehicle gel).

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, Age, and Geographic Region

Table 13 provides a descriptive analysis by race for clinical response at TOC in the PMITT population of Study MP-1601-01. Overall, the results were similar to those seen for the overall population. The results for the Others Race subgroup should be interpreted with caution due to the small sample sizes. Since all subjects were females and the mean age was 31 years and very few subjects were older than 65 years, analyses by gender and age were not conducted. Analyses by geographic region were not conducted since all clinical sites were in the United States.

Table 13
MP-1601-01
Clinical Cure at TOC by Race (PMITT)

	Metronidazole Gel 1.3% (n=250)	Vehicle Gel (n=237)
White	37/94 (39.4)	26/86 (30.2)
Black	54/149 (36.2)	35/146 (24.0)
Others	2/7 (28.6)	2/5 (40.0)

4.2 Other Special/Subgroup Populations

There are no other special/subgroup populations of interest.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

On the original case report form (CRF) for Study MP-1601-01, investigators were requested to assess vaginal discharge at the Day 7 and Day 21 visits as "Present" or "Absent". Some investigators interpreted "Present" as any discharge whether abnormal or normal thus, making it difficult to accurately assess clinical response which allowed for discharge as long as it was considered to be physiologically normal. After a number of subjects were assessed with this version of the CRF, the CRF was modified to ask the question "Has the original discharge characteristic of bacterial vaginosis returned to a normal physiological discharge?" with a "Yes" or "No" response to ensure a more accurate assessment of clinical response. Thus the PMITT population was defined based on those who were to be assessed at the Day 21 visit with the modified CRF using this criterion. The protocol was amended to change the primary efficacy analysis population from the MITT to the PMITT population. Due to the change in the primary analysis population, the total sample size randomized was increased from 570 subjects to 650 to ensure that a minimum of 366 subjects would be included in the PMITT population. At the time the modified CRF was implemented, some subjects had already been assessed at their Day 7 visit with the old version of the CRF. Therefore, the additional Day 7 Analysis population was defined for analyses of the secondary endpoints at Day 7. This is a further subset of the PMITT population.

While the PMITT population was to be defined based on those who were to be evaluated with the revised version of the CRF, the Sponsor included 8 subjects in the PMITT population enrolled prior to the amendment of the CRF because, as stated in the study report, there was sufficient information recorded in the source documentation to allow the investigator to determine a response to the revised discharge question. All 8 subjects were imputed as failures in the PMITT analysis based on the source documentation which indicated that the vaginal discharge present was abnormal. Since these subjects were not evaluated with the revised CRF (requirement for inclusion in the PMITT population) although this information was able to be assessed, there may be concerns with including such subjects in the PMITT population since not all subjects who were not evaluated with the revised CRF were able to have this information

assessed through source documentation. If these subjects were excluded from the PMITT analysis, then clinical cure rates at TOC would be 38.0% (93/245) for metronidazole vaginal gel 1.3% and 26.9% (63/234) for vehicle gel (CMH p=0.010). The difference in clinical cure rates at TOC is 11.1% with a 95% confidence interval of (2.8, 19.4). These results, however, are consistent with those seen for the PMITT population.

In order to determine whether there was an effect on the results of the primary endpoint based on the assessment of vaginal discharge, a sensitivity analysis for clinical cure was conducted on the MITT population. An assessment of vaginal discharge= "Present" was considered "Yes" and vaginal discharge= "Absent" was considered "No" in the analysis of the MITT population. The results for the MITT population were consistent with those of the PMITT population (Table 5) implying there was perhaps little impact of how vaginal discharge was evaluated on the assessment of clinical response.

Since successful response required all three criteria to be met (return to normal physiological discharge, clue cells < 20%, and negative whiff test), any impact on the assessment of clinical response of the evaluation of discharge would have been due to those subjects who were considered a failure only because of an abnormal discharge (i.e. subject had clue cells less than 20% and a negative whiff test). For those who were excluded from the PMITT population only 2 subjects in each treatment arm had only present discharge as a reason for failure. This further explains why there was little impact of how vaginal discharge was evaluated on the assessment of clinical response. However, the evaluation of discharge may have had an impact on an accurate assessment of discharge. As noted in Table 7, there was a difference between treatment groups in the percent of subjects whose discharge returned to normal. However, for those excluded from the PMITT population, the percent of subjects whose discharge was absent were similar (38.1% metronidazole vaginal gel 1.3% and 37.5% vehicle gel). It is possible that for some subjects the present discharge may have been considered a normal physiological discharge. Thus, the revision to the CRF for an accurate assessment of discharge was probably appropriate.

The primary efficacy endpoint evaluated as well as the definitions used for clinical response differ between the Phase 2 and Phase 3 trials. Between the conduct of the Phase 2 and Phase 3 trials, the Medical Division had a change in thinking as to how to evaluate the efficacy of BV trials. Therapeutic response had been the primary endpoint. Therapeutic cure requires both clinical and bacteriological cure. Clinical cure had been defined as absence of an off-white, thin, homogeneous discharge, negative whiff test, absence of clue cells, and < 4.7 vaginal fluid pH. In addition, the subject must not have received any antimicrobial drugs during the study period and the investigator must have answered no to the question "In your opinion, does the patient require additional treatment for BV infection at this time?". Following a change in thinking, the Medical Division changed the primary endpoint in BV trials to just clinical cure where clinical cure was defined as return of normal physiological discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. Due to the differences in the definition of clinical response, results from the two trials will only be discussed separately and any interpretation of cross study comparisons of clinical and therapeutic response rates should be made with caution.

5.2 Collective Evidence

Two studies were conducted to evaluate the efficacy of metronidazole vaginal gel 1.3%, a Phase 3 confirmatory trial (MP-1601-01) versus vehicle gel and a Phase 2 dose ranging study (GW05-0904) compared to metronidazole vaginal gel 0.75%. While the study populations were similar, the endpoints and the controls of the two studies differed. Therefore, the efficacy data from the studies were not integrated.

The pivotal evidence to support the efficacy of metronidazole vaginal gel 1.3% was based on the single Phase 3 trial. This trial showed that treatment with metronidazole vaginal gel 1.3% led to a statistically significant greater clinical cure at Day 21-30, the TOC visit, than treatment with the vehicle gel. The clinical cure at TOC for metronidazole vaginal gel 1.3% was 37.3% and 10.6% better than treatment with vehicle gel. Significant differences were also seen in the secondary endpoints of therapeutic cure at TOC, bacteriological cure at TOC, clinical cure at Day 7 and bacteriological cure at Day 7.

Supportive evidence comes from the Phase 2 dose ranging study. This trial showed comparable or slightly better therapeutic cure rates at TOC for each of the metronidazole vaginal gel 1.3% groups compared to metronidazole vaginal gel 0.75%. Similar conclusions were drawn for the secondary endpoints of clinical cure and bacteriological cure.

Additional supportive information for metronidazole vaginal gel 1.3% also comes from the safety and efficacy studies available for the treatment of BV with MetroGel-Vaginal 0.75% which were reviewed for the approval of NDA 20-208.

5.3 Conclusions and Recommendations

Based on the results of the single pivotal Phase 3 trial, a single dose of metronidazole vaginal gel 1.3% was shown to be more effective than vehicle gel in producing clinical cure at the TOC visit, Day 21-30. Secondary endpoints of bacteriological cure and therapeutic cure at the TOC were also significantly better for metronidazole vaginal gel 1.3% than vehicle gel. Supportive data is provided by the small dose ranging study which showed that the efficacy of a single dose of metronidazole vaginal gel 1.3% was numerically similar to a 5 day treatment with metronidazole vaginal gel 0.75%. Therefore, there is adequate evidence of efficacy to support the indication of the treatment of BV for metronidazole vaginal gel 1.3%.

5.4 Labeling Recommendations

The following labeling changes are recommended in Section 14 Clinical Studies.

- It is recommended that the Day 21 visit be referred to as the Test of Cure visit. This visit has been referred to as Day 21 by the Applicant but the visit could actually occur between Day 21 and 30.
- The Applicant is proposing to present (b) (4) Day 21 (TOC) results in Table 1. The (b) (4) and the Day 21 (TOC) rates are based on the PMITT population. To be consistent with other labels for approved BV products, it is recommended that only the Day 21 (TOC) results be included in the

table. If it is determined by Clinical that it is acceptable to include [redacted] (b) (4), then it is recommended that the results be presented for the MITT population to ensure that the rates are based on the same population. As discussed above, even though the PMITT population was to be the primary analysis population for the TOC visit, the results for the PMITT and the MITT are highly consistent and the conclusions drawn are the same.

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/s/

CHERYL A DIXON
01/21/2014

KAREN M HIGGINS
01/21/2014
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205223 **Applicant:** Valeant Pharmaceuticals **Stamp Date:** 5/24/13

Drug Name: Metronidazole Vaginal Gel 1.3% **NDA/BLA Type:** Standard

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			Analysis datasets appear to contain variables necessary to reproduce Sponsor's analyses with minimal additional programming necessary. Provided in ADAM format for the Phase 3 study.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __ Yes**_____**
If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. N/A

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the 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			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

The submission contains one pivotal phase 3 trial- MP-1601-01. MP-1601-01 was a multi-center, randomized, double-blind study to evaluate the safety and efficacy of a single intravaginal dose of metronidazole vaginal gel 1.3% compared to a single intravaginal dose of vehicle gel in treating female subjects with bacterial vaginosis. The primary efficacy endpoint was clinical response at Day 21. Secondary endpoints include clinical cure at Day 7, bacteriological cure at Day 7 and 21, therapeutic cure at Day 7 and 21, and time to resolution of symptoms. Based on the Applicant's summary of the results, clinical cure at Day 21 was statistically significantly higher for patients receiving metronidazole vaginal gel 1.3% compared to patients receiving vehicle gel. Similar results were shown for the secondary endpoints.

Supportive efficacy data comes from a small Phase 2 dose ranging study- GW05-0904. GW05-0904 evaluated the safety and efficacy of metronidazole vaginal gel 1.3% administered once daily for 1, 3, or 5 days compared with MetroGel Vaginal 0.75% administered once daily for 5 days. The primary efficacy endpoint was therapeutic response at test of cure (Day 21 to 30). Based on the Applicant's summary of the results, a single dose of metronidazole vaginal gel 1.3% demonstrated similar efficacy to 5 days of treatment with MetroGel Vaginal 0.75%.

Cheryl Dixon, Ph.D.	7/2/13
Reviewing Statistician	Date
Karen Higgins, Sc.D.	7/2/13
Supervisor/Team Leader	Date

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/s/

CHERYL A DIXON
07/08/2013

KAREN M HIGGINS
07/10/2013