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APPLICATION NUMBER:

205223Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: 205223

Submission Date(s): May 24, 2013

Applicant: Valeant Pharmaceuticals North America LLC

Product: Metronidazole Vaginal Gel 1.3%

Reviewer: Hala Shamsuddin, M.D.

Date of Review: February 24, 2014

Covered Clinical Study (Name and/or Number):
Study GW05-0904
Study MP-1601-01

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 52 (fifty-two)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 52 (fifty-two)		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	NA	No ☐ (Request explanation

		from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Reviewer's Comments
Certification was submitted that the sponsor had not entered into any financial arrangements with any of the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR 54.2(a). Certification was provided that none of the listed investigator disclosed a proprietary interest in the product or significant equity in the sponsor as defined in 21 CFR 54.2(b) and (c), and that no listed investigator received significant payments of other sorts 21CFR (f).

The applicant for NDA 205223 has adequately disclosed financial interests/arrangements with the clinical investigators.

[1] See [web address].

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/s/

HALA H SHAMSUDDIN
03/04/2014

Clinical Review

NDA	205223 SN 000
Type of Review	Standard
Submit Date	May 24, 2103
PDUFA Goal Date	March 24, 2014
Division/Office	Division of Anti-Infective Products (DAIP) Office of Anti-microbial Products (OAP)
Reviewer	Hala Shamsuddin MD
Team Leader	Thomas Smith MD
Product	Metronidazole Vaginal Gel 1.3%
Proposed Trade Name	Metronidazole Vaginal Gel 1.3%
Sponsor	Valeant Pharmaceuticals
Indication	Treatment of Bacterial Vaginosis in Non-Pregnant Women

Contents

Recommendation on Regulatory Action

The recommendation is to approve metronidazole vaginal gel 1.3% single administration for the treatment of women with bacterial vaginosis (BV).

Risk Benefit Assessment

The benefits of therapy outweigh the risks.

Metronidazole vaginal gel 1.3% single dose was superior to vehicle for the primary endpoint of clinical cure at Day 21, and for the secondary endpoints of clinical cure on Day 7, bacteriologic cure on Days 7 and 21 and therapeutic cure on Day 21. Metronidazole gel also resulted in faster time to symptom resolution compared to vehicle.

Main adverse events included vaginal candidiasis, vulvo-vaginal pruritus, diarrhea, nausea and headache. The AE profile was similar to the AE profile of the approved 0.75% metronidazole gel.

Metronidazole is pregnancy category B. Systemic exposure resulting from the 1.3% gel is substantially lower than systemic exposure resulting from oral metronidazole.

Recommendations for Post-Market Risk Evaluation and Mitigation Strategies

None

Recommendations for Post-Market Requirements and Commitments

One postmarketing requirement is recommended: A study to evaluate the safety of metronidazole gel 1.3% single dose in the treatment of bacterial vaginosis in females 12-<18 years of age.

Executive Summary

Introduction

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of childbearing age. Clinical diagnosis is based on the presence of three of four criteria (Amsel's Criteria): abnormal vaginal discharge, positive whiff test, vaginal pH >4.5, and ≥20% clue cells on the saline wet mount. Bacteriologically, BV is characterized by a decrease of the normally present *Lactobacillus* species and an overgrowth of

normally present *Gardnerella vaginalis*, *Bacteroides* and *Prevotella* species, anaerobic gram-positive cocci, *Mobiluncus* species and *Mycoplasma hominis* in vaginal secretions. The relative numbers of *Lactobacillus* and *Gardnerella/Bacteroides* morphotypes seen per high power field on microscopic exam of a Gram stain of vaginal secretion is used to generate the Nugent score. A score of 7-10 is indicative of BV. A score of 4-6 is considered intermediate and a score of 0-3 is considered normal.

Metronidazole vaginal gel and vaginal cream 0.75%, clindamycin vaginal cream 2%, extended release oral metronidazole and oral tinidazole are FDA approved for the treatment of BV. While other formulations of oral metronidazole are not FDA approved for this indication, they are commonly used and are CDC-recommended as first line therapies.

Efficacy

In support of this NDA application, the sponsor conducted one dose-ranging Phase 2 trial, one pivotal placebo-controlled Phase 3 trial and one PK trial.

A single 1.3% metronidazole vaginal gel administration resulted in systemic exposure that was similar to the systemic exposure following a single 0.75% single dose administration as reported in the product labeling of the approved 0.75% product.

The dose-ranging Phase 2 trial (trial GW-05-0904) was a randomized trial that compared metronidazole vaginal gel 1.3% single dose to 1.3% gel administered for 3 or 5 days and to the approved regimen of 0.75% gel for 5 days in women with BV. The primary endpoint was therapeutic cure (clinical plus bacteriologic cure) at Day 21. Clinical cure was defined as resolution of the Amsel criteria present at diagnosis and a no answer to the question “does the patient require additional treatment for BV infection at this time?” Bacteriologic cure was defined as a Nugent score < 4.

The 1.3% single dose and the approved 0.75% regimen resulted in similar cure rates, similar time to resolution of symptoms and a similar safety profile.

Table 1: Cure Rates at Day 21 – MITT - Study GW05-0904

	Metronidazole Gel			
	0.75% x 5 days N = 49	1.3% x 1 day N = 43	1.3% x 3 days N = 48	1.3% x 5 days N = 49
Therapeutic cure 95% CI	12 (20.3%) (11.0, 32.8)	15 (25.4%) (15.0, 38.4)	12 (22.2%) (12.0, 35.6)	17 (30.4%) (18.8, 44.1)
Clinical Cure 95% CI	17 (28.8%) (17.8, 42.1)	18 (30.5%) (19.2, 43.9)	17 (31.5%) (19.5, 45.6)	23 (41.1%) (28.1, 55)
Bacteriologic Cure 95% CI	18 (30.5%) (19.2, 43.9)	18 (30.5%) (19.2, 43.9)	18 (33.3%) (21.1, 47.5)	26 (46.4%) (33.0, 60.3)

The Phase 3 trial (MP-1601-01) was a randomized, double-blind trial that compared metronidazole gel 1.3% single dose to vehicle in women with BV. As advised by the

FDA, the primary endpoint was clinical cure at Day 21, defined as return of physiologic vaginal discharge confirmed by the investigator with a negative whiff test and clue cells < 20% (no pH criterion). Bacteriologic and therapeutic cure at Days 7 and 21 were secondary endpoints. Clinical cure at Day 7 and time to resolution of symptoms were also secondary endpoints.

The MITT population included all randomized subjects who had negative tests for *N. gonorrhoeae* and *C. trachomatis* and had a Nugent score ≥4 at Visit 1. For the classification of clinical response, vaginal discharge was initially indicated as "present" or "absent" on the CRF. Because the response to this question was equivocal, the question was modified to a Yes or No answer to the question "has the original discharge characteristic of BV returned to a normal physiologic discharge?" The Primary Modified ITT population was defined as the subset of the MITT population who were evaluated on D 21 using the above yes or no question on the CRF. The PMITT population was the primary analysis population.

Subjects in the MITT, PMITT, PP and safety populations were matched as to age, race, previous BV history and Nugent score. Metronidazole gel 1.3% was superior to placebo in the MITT, PMITT and PP populations for the primary endpoint of clinical cure at Day 21, and the secondary endpoints of clinical cure at Day 7, bacteriologic cure at Days 7 and 21 and therapeutic cure at Days 7 and 21. Metronidazole gel also resulted in more rapid resolution of symptoms.

Table 2: Summary of Efficacy Results on Day 21 – MP-1601-01

PMITT				
	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH	P value
Clinical Cure Day 21 (95% CI)	93 (37.2%) (31.2%, 43.5%)	63 (26.6%) (21.1%, 32.7%)	10.6% (2.4%, 18.8%)	0.010
Bacteriologic Cure Day 21 (95% CI)	47 (18.8%) (14.2%, 24.2%)	19 (8.0%) (4.9%, 12.2%)	10.8% (4.8%, 16.7%)	< 0.001
Therapeutic Cure Day 21 (95% CI)	42 (16.8%) (12.4%, 22.0%)	17 (7.2%) (4.2%, 11.2%)	9.6% (3.9%, 15.3%)	< 0.001
MITT				
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Clinical Cure Day 21 (95% CI)	108 (37.0%) (31.4%,42.8%)	76 (26.7%) (21.1%, 32.7%)	10.3% (2.8%, 17.9%)	0.007
Bacteriologic Cure Day 21 (95% CI)	57 (19.5%) (15.1%, 24.5%)	22 (7.7%) (4.9%, 11.5%)	11.8% (6.3%, 17.3%)	< 0.001
Therapeutic Cure Day 21 (95% CI)	49 (16.8%) (12.7%, 21.6%)	18 (6.3%) (3.8%, 9.8%)	10.5% (5.3%, 15.6%)	< 0.001
PP				
	MVG 1.3% N = 214	Vehicle N = 204	Difference MVG-VEH	P value
Clinical Cure Day 21 (95% CI)	87 (40.7%) (34.0%, 47.6%)	61 (29.9%) (23.7%, 36.7%)	10.8% (1.7%, 19.9%)	0.007

Bacteriologic Cure Day 21 (95% CI)	44 (20.6%) (15.1%, 26.0%)	14 (6.9%) (3.4%, 10.3%)	13.7% (7.0%, 20.4%)	< 0.001
Therapeutic Cure Day 21 (95% CI)	39 (18.2%) (13.1%, 23.4%)	15 (7.4%) (3.8%, 10.9%)	10.8% (4.7%, 16.9%)	< 0.001

Safety

Adverse events that occurred in ≥1% of subjects in either arm included diarrhea, nausea, headache, dysmenorrhea, vulvo-vaginal candidiasis (VVC) and vulvo-vaginal pruritus. AEs that occurred more frequently in the metronidazole gel arm were VVC, VV pruritus, vaginal hemorrhage and dysmenorrhea.

Table 3: AEs occurring in ≥1% of subjects – Study MP-1601-01

MedDRA v. 14.0	MVG 1.3% N = 321	Vehicle N = 316
Any AE	61 (19.0%)	51 (16.1%)
Gastrointestinal	15 (4.7%)	16 (5.1%)
Diarrhea	4 (1.2%)	5 (1.6%)
Nausea	5 (1.6%)	5 (1.6%)
Infection/Infestation	26 (8.1%)	17 (5.4%)
VVC	18 (5.6%)	10 (3.2%)
Nervous System	8 (2.5%)	4 (1.3%)
Headache	7 (2.2%)	4 (1.3%)
Reproductive/Urinary	17 (5.3%)	16 (5.1%)
Dysmenorrhea	4 (1.2%)	1 (0.3%)
VV pruritus	5 (1.6%)	5 (1.6%)

Overall, 510 subjects received any dose of metronidazole gel 1.3% in Studies MP-1601-01 and GW05-0904. Adverse Events noted in ≥1% of subjects who received any regimen of metronidazole gel 1.3% included abdominal pain, diarrhea, nausea, VVC, nasopharyngitis, headache, dysmehorrhea, vulvo-vaginal burning and vulvo-vaginal pruritus. Adverse Events noted more frequently in the 1.3% gel recipients compared to vehicle recipients included abdominal pain, headache, VVC, nasopharyngitis, dysmenorrhea, vulvo-vaginal burning and vulvo-vaginal pruritus.

Table 4: Adverse Events Occurring in ≥1% of BV Subjects who Received Metronidazole Gel 1.3%, 0.75% or Vehicle – Studies MP 1601-01 and GW05-0904

	Any MVG 1.3% N = 510	MVG 0.75% N = 65	Vehicle N = 316
Any AE	125 (24.5%)	28 (43.1%)	51 (16.1%)
Gastrointestinal	28 (5.5%)	3 (4.6%)	16 (5.1%)
Abdominal Pain	9 (1.8%)	0	2 (0.6%)
Diarrhea	5 (1.0%)	0	5 (1.6%)
Nausea	10 (2.0%)	0	5 (1.6%)
Infection/Infestation	40 (7.8%)	14 (21.5%)	17 (5.4%)
Trichomoniasis	0	2 (3.1%)	2 (0.6%)
UTI	2 (0.4%)	2 (3.1%)	0
VVC	34 (6.7%)	9 (13.8%)	10 (3.2%)

Nasopharyngitis	7 (1.4%)	1 (1.5%)	2 (0.6%)
Nervous System	29 (5.7%)	11 (16.9%)	4 (1.3%)
Headache	22 (4.3%)	11 (16.9%)	4 (1.3%)
Reproductive/Urinary	17 (3.3%)	8 (12.3%)	16 (5.1%)
Dysmenorrhea	8 (1.6%)	0	1 (0.3%)
Pelvic pain	3 (0.6%)	3 (4.6%)	2 (0.6%)
VV burning	7 (1.4%)	3 (4.6%)	2 (0.6%)
VV pruritus	11 (2.2%)	1 (1.5%)	5 (1.6%)

Pregnancy

Metronidazole is pregnancy category B. Three pregnancies were reported in each of the Phase 2 and 3 studies. In the dose-ranging study, 2 pregnancies occurred in the 0.75% for 5 days arm and one in the 1.3% for 5 days arm. The pregnancy outcomes were abruptio placenta and premature delivery at week 24 of gestation with fetal death and marked chorioamnionitis, spontaneous abortion at week 16 of gestation, and a blighted ovum at week 4.5 gestation treated with dilation and curettage. The narratives did not specify whether these women had cured BV or not. Two of the pregnancies in the Phase 3 study occurred in vehicle recipients and one in metronidazole gel recipient. Outcome was known for one of the vehicle recipients: delivery at week 36 gestation with oligohydramios and no fetal anomalies.

Introduction

Bacterial Vaginosis

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of childbearing age. BV symptoms, when present, include a thin fishy malodorous vaginal discharge. Diagnosis is based on the presence of three of four criteria (Amsel's Criteria): abnormal vaginal discharge, positive whiff test, vaginal pH >4.5, and ≥20% clue cells on the saline wet mount.

Bacteriologically, BV is characterized by a decrease of the normally present *Lactobacillus* species and an overgrowth of normally present *Gardnerella vaginalis*, *Bacteroides* and *Prevotella* species, anaerobic gram-positive cocci, *Mobiluncus* species and *Mycoplasma hominis* in vaginal secretions. The relative numbers of *Lactobacillus* and *Gardnerella/Bacteroides* morphotypes seen per high power field on microscopic exam of a Gram stain of vaginal secretion is used to generate the Nugent score as follows:

Table 5: Nugent Scoring System for Gram Stain of Vaginal Smears

Lactobacillus	Score	*Gardnerella Bacteroides*	Score	Curved Gram variable rods	Score	Total Score
≥30	0	0	0	0	0	0
5-30	1	<1	1	< 1	1	3

1-4	2	1-4	2	1-4	1	5
< 1	3	5-30	3	5-30	2	8
0	4	≥30	4	≥30	2	10

Nugent score of at least 7 is indicative of BV. A score of 4-6 is considered intermediate and a score of 0-3 is considered normal.

Currently Available Treatments for BV

The CDC recommended therapies for BV include topical or oral metronidazole, topical or oral clindamycin, or oral tinidazole[1].

Table 6: CDC Recommended Treatments for BV - 2010 Treatment Guidelines

Recommended Treatments	Alternative Treatments	Additional Treatments
Metronidazole 500 mg orally twice a day for 7 days,	Tinidazole 2 g orally daily for 2 days,	Metronidazole extended release (ER) 750 mg once daily for 7 days
OR	OR	OR
Metronidazole gel 0.75% one full applicator (5g) intravaginally once a day for 5 days,	Tinidazole 1 g orally once daily for 5 days	A single dose of clindamycin intravaginal cream
OR	OR	
Clindamycin cream 2% one full applicator (5g) intravaginally at bedtime for days	Clindamycin 300 mg orally twice daily for 7 days OR	
	OR	
	Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days	

Of the CDC recommended therapies, metronidazole vaginal gel 0.75%, extended release oral metronidazole tablets, tinidazole tablets, clindamycin vaginal cream and clindamycin vaginal suppository are FDA approved for the treatment of BV. Other oral preparations of metronidazole and oral clindamycin are not FDA approved for this indication but are marketed for other indications.

Regulatory Background

The Phase 2 dose-ranging study was conducted by Graceway Pharmaceuticals under IND 107,484. Graceway proposed a Phase 3 trial with the objective of demonstrating that metronidazole vaginal gel 1.3% given for one day was non-inferior to the currently approved regimen of MetroGel-Vaginal 0.75% for 5 days by a non-inferiority margin of 15%. In an EOP-2 meeting, the FDA's advice was to conduct a placebo-controlled study

[1] http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf

in lieu of the proposed non-inferiority trial. In addition, the FDA agreed that should the placebo-controlled Phase 3 study provide convincing evidence of efficacy, the previous findings of efficacy of the 0.75% metronidazole formulations in the treatment of BV may be used as supportive evidence for filing an NDA.

The IND was transferred from Graceway to Medicis Pharmaceuticals on December 2, 2011. On February 8, 2012, Medicis submitted the placebo-controlled Phase 3 protocol MP-160-01 for Special Protocol Assessment. The primary endpoint was the proportion of subjects with (b) (4)

In a fax communication dated March 26, 2012, the FDA recommended clinical cure as the primary efficacy endpoint, defined as return of normal physiological discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. On April 23, 2012, the sponsor submitted a revised protocol that incorporated the newly recommended endpoint.

Ethics

All studies were conducted in accordance with Good Clinical Practice. The study protocols and informed consents were reviewed and approved by IRBs, primarily the (b) (4), plus local IRBs. Financial disclosures were submitted.

Issues Related to Other Review Disciplines

CMC

The sponsor references NDA 20-208, MetroGel-Vaginal 0.75%. In comparison with the 0.75% gel, the 1.3% gel contains polyethylene glycol 400, benzyl alcohol, and polycarbophil. (b) (4)

The product will be supplied in a pre-filled applicator containing 65 mg metronidazole. In comparison, the pre-filled applicator for the 0.75% marketed product contains 37.5 mg metronidazole.

Microbiology

Metronidazole is a nitroimidazole antibacterial and antiprotozoal agent. It is active against most obligate anaerobic gram positive and gram negative bacteria, *Trichomonas, Entamoeba histolytica and Giardia lamblia*. The exact mechanism of action is unknown, but likely involves reduction by low-redox potential electron transport proteins with the

resultant reactive species causing DNA disruption and inhibition of nucleic acid synthesis.

Toxicology

The sponsor references NDA 20-208 and the corresponding IND 29,298 for MetroGel-Vaginal 0.75% for nonclinical toxicology studies in rats and rabbits. The sponsor also references NDA 20-208 for mutagenicity and reproductive toxicity studies.

The sponsor performed a 10 day GLP compliant intravaginal toxicology study in rabbits using metronidazole vaginal gel 1.3%, vehicle gel, MetroGel Vaginal 0.75%, a positive control (2% Nonoxynol-9), and a sham control at the maximum feasible dose volume (1 ml). The sham control animals experienced minimal irritation at necropsy. All other animals experienced mild vaginal irritation.

Clinical Pharmacology

According to the product labeling of 0.75% metronidazole vaginal gel (Vandazole®), a single 5 gm intravaginal dose of 0.75% gel administered to healthy subjects results in mean serum Cmax 281 ng/mL (range 134 to 464), and mean AUC 5989 ng•hr/mL. Tmax is 9.5 hours (range 4 to 17 hours). Multiple 5 gm intravaginal doses of 0.75% administered to patients with BV results in mean serum Cmax 214 ng/mL on day 1, and 294 ng/mL on day 5.

In comparison, a single 500 mg oral dose of metronidazole results in mean serum Cmax of 12,785 ng/mL (range 10,013 to 17,400) and mean AUC 125,000 ng•hr/mL in the same subjects.

Sources of Clinical Data

Table 7: Studies Conducted to Evaluate the Safety and Efficacy of Metronidazole Vaginal Gel 1.3%

	Study Design	Study Arms	N
MP-1601-02	PK study Healthy volunteers	Metronidazole vaginal gel 1.3% single dose	20
GW05-0904	Randomized, investigator blinded, dose ranging	Metronidazole vaginal gel 1.3% for 1, 3 or 5 days Metronidazole vaginal gel 0.75% for 5 days	255
MP-1601-01	Randomized, double blind, vehicle control	Metronidazole vaginal gel 1.5% single dose Vehicle Control	651

PK Study MP-1601-02

This was a PK study conducted in healthy women volunteers in the United States.

20 adult women 18-40 years of age received a single intravaginal 5 gm dose of Metronidazole Vaginal Gel 1.3%. The mean serum metronidazole Cmax was 238.95 ng/mL +/- 90.16 (range 113.93 to 428.44), and the mean AUC0-t was 5359.57 +/- 2769.35 ng.h/mL. Average Tmax was 7.31 +/- 3.13 hours (range 3.2 to 18 hours) after dosing, and the average half-life was 9.65 hours.

Reviewer's Comments
Systemic exposure following a single administration of metronidazole gel 1.3% in healthy women is similar to the systemic exposure following a single administration of metronidazole gel 0.75%, and considerably lower compared to orally administered metronidazole.

Adverse Events
There were no serious adverse events and no subject discontinued the study due to an AE.

Table 8: Adverse Events – Study MP-1601-02

MedDRA version 14.0	MVG 1.3% 20
Any AE	2 (10.0%)
Gastrointestinal Nausea	1 (5.0%) 1 (5.0%)
General/Administration Site Vessel puncture hematoma	1 (5.0%) 1 (5.0%)
Nervous System Headache	1 (5.0%) 1 (5.0%)

Phase 2 Dose Ranging Study - Study GW05-904

Study Design

This was a multicenter, randomized, investigator-blinded study comparing the efficacy and safety of metronidazole vaginal gel 1.3% administered once a day for one, three, or five days to MetroGel-Vaginal 0.75% administered for 5 days in the treatment of BV. The study was conducted at 20 centers in the United States between April 26, 2010 and September 23, 2010.

Non-pregnant women at least 18 years of age with a diagnosis of BV, defined as satisfying all of Amsel criteria (abnormal thin homogenous vaginal discharge, clue cells ≥ 20% of the total epithelial cells on wet mount, pH of vaginal fluid ≥ 4.5, and positive 10% KOH whiff test), were enrolled. Subjects had to agree to abstain from sexual intercourse throughout the first 7 days of the study and to use a non-lubricated condom after that. Subjects also had to abstain from drinking alcohol during the treatment period and for one day afterward, and to refrain from using intravaginal products for the duration of the study.

Pregnant and lactating women, women menstruating at the time of diagnosis, women who had known or suspected other causes of vaginitis, who had received an antifungal or antimicrobial therapy within the previous 14 days, who had taken disulfiram, who had a history of hypersensitivity to metronidazole, who had an immunodeficiency, who were treated for cervical intra epithelial neoplasia or cervical carcinoma, who were using Coumadin or steroids were excluded.

Pregnancy test, Gram stain for Nugent score, rapid test for *T. vaginalis* antigen, wet mount (for clue cells, *T. vaginalis* and *Candida*) and nucleic acid test for *C. trachomatis* and *N. gonorrhoeae* were obtained at screening and at Day 21-30 (TOC visit). A Pap smear was obtained at screening if the subject did not have one documented within the past 12 months. Subjects were evaluated by phone call on days 8 to 10, but were instructed to call the study investigator is symptoms did not improve within 3 to 4 days and were given a diary to record symptoms.

The primary endpoint was therapeutic cure, defined as clinical and bacteriologic cure, at Day 21. Clinical cure was defined as resolution the Amsel criteria present at diagnosis. In addition, the subject should 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?” Bacteriologic cure was defined as a Nugent score < 4.

The secondary endpoints were the proportion of subjects with clinical cure, the proportion of subjects with bacteriologic cure, time to resolution of symptoms, return of symptoms, leakage of study drug and subject questionnaire regarding treatment satisfaction.

The ITT population included all randomized subjects. The MITT included all randomized subjects who received study medication, returned for at least 1 post-baseline visit, had a negative test for *N. gonorrhoeae* and *C. trachomatis*, and a Gram stain Nugent score ≥ 4 at visit 1. Subjects with missing primary efficacy data were considered failures. The MITT population was used for supportive efficacy analyses.

The PP population included subjects in MITT who satisfied all inclusion and exclusion criteria, had no protocol violations, started the study medication within 1-2 days of randomization, were compliant with study medication, had no antimicrobial use during

study period, did not use additional intravaginal products during the study period, had the TOC Nugent score within days 21-30 of the first day of treatment. The PP population was used for primary efficacy analysis.

The safety population included all randomized subjects who applied any amount of study medication.

Subject Disposition

255 subjects were randomized. 254 subjects were included in the safety population.

Table 9: Subject Disposition – Study GW05-0904

	Metronidazole Gel				
	0.75% x 5 days	1.3% x 1 day	1.3% x 3days	1.3% x 5days	Total
Randomized	66	65	60	64	255
Treated	65 (98.5%)	65 (100%)	60 (100%)	64 (100%)	254
Completed	59 (89.4%)	57 (87.7%)	55 (91.7%)	63 (98.4%)	234 (91.8%)
Discontinued	7 (10.6%)	8 (12.3%)	5 (8.3%)	1 (1.6%)	21 (8.2%)
Reason for D/C					
Investigator	0	1 (1.5%)	0	0	1 (0.4%)
Subject Request	0	0	1 (1.7%)	0	1 (0.4%)
Non Compliance	1 (1.5%)	0	0	0	1 (0.4%)
Lost to Follow	1 (1.5%)	4 (6.2%)	3 (5.0%)	1 (1.6%)	9 (3.5%)
GC or Chlamydia	4 (6.1%)	1 (1.5%)	0	0	5 (2.0%)
Failure of Rx	1 (1.5%)	2 (3.1%)	1 (1.7%)	0	4 (1.6%)
AE	0	0	0	0	0

Analysis Populations

The MITT population included 228 subjects and PP included 189 subjects.

Table 10: Analysis Populations - Study GW05-0904

	Metronidazole Gel				
	0.75% x 5 days	1.3% x 1 day	1.3% x3 days	1.3% x 5 days	Total
ITT	66	65	60	64	255
Safety	65 (98.5%)	65 (100%)	60 (100%)	64 (100%)	254
MITT	59 (89.4%)	59 (90.8%)	54 (90.0%)	56 (97.5%)	228 (89.4%)
Excluded from MITT	7 (10.6%)	6 (9.2%)	6 (10.0%)	8 (12.5%)	27 (10.6%)
Reasons for MITT exclusion GC or Chlamydia Nugent <4	 4 (6.1%) 4 (6.1%)	 1 (1.5%) 5 (7.7%)	 0 6 (10.0%)	 0 8 (12.5%)	 5 (2.0%) 23 (9.0%)
PP	49 (74.2%)	43 (66.2%)	48 (80.0%)	49 (76.6%)	189 (74.1%)
Excluded from PP	17 (25.8%)	22 (33.8%)	12 (20.0%)	15 (23.4%)	66 (25.9%)

Reasons for PP exclusion					
Did not start med on time	4 (6.1%)	5 (7.7%)	4 (6.7%)	1 (1.6%)	14 (5.5%)
Non-compliant	6 (9.1%)	7 (10.8%)	4 (6.7%)	2 (3.1%)	19 (7.5%)
Used other antimicrobial	4 (6.1%)	3 (4.6%)	1 (1.7%)	2 (3.1%)	10 (3.9%)
Used other vaginal product	0	1 (1.5%)	0	1 (1.6%)	2 (0.8%)
Nugent not within 21-30 d	10 (15.2%)	12 (18.5%)	4 (6.7%)	4 (6.7%)	30 (11.8%)

Demographics and Disease Characteristics

Table 11: Subject Demographics and Disease Characteristics– ITT - Study GW05-0904

	Metronidazole Gel			
	0.75% x 5days N = 66	1.3% x 1day N = 65	1.3% x3days N = 60	1.3% x 5days N - 64
Age, mean (SD)	35.0 (9.3)	35.0 (10.1)	33.0 (9.0)	37.4 (10.9)
Age Range (years)	19-60	19-66	18-59	21-67
Race				
White	33 (50.0%)	33 (50.8%)	27 (45.0%)	28 (43.8%)
Black	32 (48.5%)	32 (49.2%)	32 (53.3%)	36 (56.3%)
Other	1 (1.5%)	0	1 (1.7%)	0
Ethnicity				
Hispanic	12 (18.2%)	9 (13.8%)	10 (16.7%)	15 (23.4%)
Non-Hispanic	54 (81.8%)	56 (86.2%)	50 (83.3%)	49 (76.6%)
Previous BV	23 (34.8%)	27 (41.7%)	25 (41.7%)	20 (31.3%)

Primary Efficacy Endpoint

The primary efficacy endpoint was therapeutic cure at Day 21-30 in the PP population.

Table 12: Cure Rates - PP population - Study GW05-0904

	Metronidazole Gel			
	0.75% x 5 days N = 49	1.3% x 1 day N = 43	1.3% x 3 days N = 48	1.3% x 5 days N = 49
Therapeutic Cure 95% CI	10 (20.4%) (10.2, 34.3)	13 (30.2%) (17.2, 46.1)	12 (25.0%) (13.6, 39.6)	16 (32.7%) (19.9, 47.5)
Clinical Cure 95% CI	14 (28.6%) (16.6, 43.3)	16 (37.2%) (23.0, 53.3)	17 (35.4%) (22.2, 50.5)	22 (44.9%) (30.7, 59.8)
Bacteriologic Cure 95% CI	15 (30.6%) (18.3, 45.4)	13 (30.2%) (17.2, 46.1)	17 (35.4%) (22.2, 50.5)	23 (46.9%) (32.5, 61.7)

Table 13: Cure Rates – MITT - Study GW05-0904

	Metronidazole Gel			
	0.75% x 5 days N = 49	1.3% x 1 day N = 43	1.3% x 3 days N = 48	1.3% x 5 days N = 49
Therapeutic cure 95% CI	12 (20.3%) (11.0, 32.8)	15 (25.4%) (15.0, 38.4)	12 (22.2%) (12.0, 35.6)	17 (30.4%) (18.8, 44.1)
Clinical Cure 95% CI	17 (28.8%) (17.8, 42.1)	18 (30.5%) (19.2, 43.9)	17 (31.5%) (19.5, 45.6)	23 (41.1%) (28.1, 55)

Bacteriologic Cure 95% CI	18 (30.5%) (19.2, 43.9)	18 (30.5%) (19.2, 43.9)	18 (33.3%) (21.1, 47.5)	26 (46.4%) (33.0, 60.3)

Table 14: Therapeutic Cure Rates by Age, Race, Ethnicity, History of Previous BV – PP - Study GW05-0904

Metronidazole Gel				
	0.75% x 5days N = 49	1.3% x 1day N = 43	1.3% x3days N = 48	1.3% x 5days N = 49
Age < 35 yrs	4/24 (16.7%)	8/26 (30.8%)	4/29 (13.8%)	0/21 (42.9%)
Age ≥ 35 yrs	6/25 (24.0%)	5/17 (29.4%)	8/19 (42.1%)	3/28 (25.0%)
White Black	7/23 (30.4%) 3/26 (11.5%)	10/23 (43.5%) 3/20 (15.0%)	5/23 (21.7%) 7/25 (28.0%)	5/20 (25.0%) 11/29 (37.9%)
Hispanic Non-Hispanic	1/8 (12.5%) 9/41 (22.0%)	3/5 (60.0%) 10/38 (26.3%)	2/8 (25.0%) 10/40 (25.0%)	5/11 (45.5%) 11/38 (28.9%)
Previous BV	5/18 (27.8%)	6/21 (28.6%)	3/19 (15.8%)	6/16 (37.5%)

Secondary Efficacy Endpoints

Secondary efficacy endpoints were clinical and bacteriologic cures at Day 21-30, time to resolution of symptoms, relapse of symptoms, drug leakage and subject treatment satisfaction.

Table 15: Time to Resolution of Symptoms – PP - Study GW05-0904

Metronidazole Gel				
	0.75% x 5days N = 49	1.3% x 1day N = 43	1.3% x3days N = 48	1.3% x 5days N = 49
Subjects Resolved	26 (53.1%)	25 (58.1%)	29 (60.4%)	28 (57.1%)
Median days Range	6 1-9	5 1-9	5 1-9	5 1-8

Table 16: Symptom Relapse – PP - Study GW05-0904

Metronidazole Gel				
	0.75% x 5days N = 49	1.3% x 1day N = 43	1.3% x3days N = 48	1.3% x 5days N = 49
Subjects Resolved	26	25	29	28
Relapsed	13/26 (50.0%)	13/25 (52.0%)	17/29 (58.6%)	6/28 (21.4%)

Table 17: Leakage of Study Drug – PP - Study GW05-0904

Metronidazole Gel				
	0.75% x 5days N = 49	1.3% x 1day N = 43	1.3% x3days N = 48	1.3% x 5days N = 49
No leakage	13 (26.5%)	7 (16.3%)	5 (10.4%)	9 (18.4%)
Minimal Amount	26 (53.1%)	18 (41.9%)	23 (47.9%)	18 (36.7%)
Moderate Amount	8 (16.3%)	10 (23.3%)	14 (29.2%)	14 (28.6%)
Large Amount	2 (4.1%)	7 (16.3%)	6 (12.5%)	7 (14.3%)
Missing	0	1 (2.3%)	0	1 (2.0%)

The majority of subjects rated the treatments as easy or very convenient to use, with the highest proportion rating the 1 day therapy as the most convenient.

Efficacy Conclusions
Metronidazole vaginal gel 1.3% given for one day and the approved regimen of 0.75% gel for 5 days resulted in similar therapeutic cure, clinical cure, bacteriologic cure, time to resolution of symptoms and symptom relapse. This regimen was chosen for Phase 3 study.

Safety Evaluation

Extent of Exposure

Table 18: Mean days of study drug exposure – Study GW05-0904

Metronidazole gel				
	0.75% x 5 d N = 65	1.3% x 1 day N = 65	1.3% x 3 days N = 60	1.3% x 5 days N = 64
Mean (SD)	4.9 (0.53)	1.2 (1.27)	3.0 (0.00)	5.1 (0.76)

Two subjects in the 1.3% x 1 day group took the drug for 5 days.

Concomitant Medications

164 subjects (64.3%) reported using at least one concomitant medication, most commonly analgesics. 16 subjects (6.3%) reported using oral fluconazole to treat vulvo-vaginal candidiasis (VVC).

Adverse Events

92 subjects (36.2%) reported at least one AE. No subject discontinued the study due to an AE. One subject in the 1.3% for 1 day group experienced a serious AE (hypoglycemia). There were no deaths.

Table 19: Summary of AE – Study GW05-0904

Metronidazole Gel				
	0.75% x 5 N = 65	1.3% x 1 N = 65	1.3% x 3 N = 60	1.3% x 5 N = 64
Subjects with any AE	28 (43.1%)	23 (35.4%)	19 (31.7%)	22 (34.4%)
Subjects with serious AE	0	1 (1.5%)	0	0

Table 20: Adverse Events – Study GW05-0904

Metronidazole Gel				
MedDRA v. 14.0	0.75% x 5 N = 65	1.3% x 1 N = 65	1.3% x 3 N = 60	1.3% x 5 N = 64
Blood and Lymphatics Anemia	0	**2 (3.1%)** 2 (3.1%)	0	**1 (1.6%)** 0

Lymphadenopathy		0		1 (1.6%)
Gastrointestinal	**3 (4.6%)**	**3 (4.6%)**	**4 (6.7%)**	**6 (9.4%)**
Abdominal distension	1 (1.5%)	0	0	0
Abdominal discomfort	1 (1.5%)	1 (1.5%)	1 (1.7%)	0
Abdominal pain	1 (1.5%)	0	3 (5.0%)	2 (3.1%)
Abdominal pain, upper	0	1 (1.5%)	0	1 (1.6%)
Constipation	0	0	0	1 (1.6%)
Diarrhea	1 (1.5%)	0	0	1 (1.6%)
Dyspepsia	1 (1.5%)	0	1 (1.7%)	0
Flatulence	1 (1.5%)	0	0	0
GE reflux	0	0	0	1 (1.6%)
Nausea	0	1 (1.5%)	0	4 (6.2%)
General/Admin Site		**2 (3.1%)**		**1 (1.6%)**
Fatigue	0	0	0	1 (1.6%)
Influenza-like		1 (1.5%)		0
Pyrexia		1 (1.5%)		0
Immune Disorders	**1 (1.5%)**	0	0	**2 (3.1%)**
Seasonal allergy	1 (1.5%)	0		2 (3.1%)
Infection/Infestation	**14 (21.5%)**	**13 (20.0%)**	**14 (23.3%)**	**6 (9.4%)**
Bronchitis	0	0	0	1 (1.6%)
Furuncle	0	0	0	1 (1.6%)
Genital Herpes	0	0	1 (1.7%)	0
Influenza	0	0	0	1 (1.6%)
Nasopharyngitis	1 (1.5%)	3 (4.6%)	3 (5.0%)	1 (1.6%)
Sinusitis	0	0	2 (3.3%)	0
UTI	2 (3.1%)	0	1 (1.7%)	1 (1.6%)
Vaginal candidiasis	9 (13.8%)	8 (12.3%)	8 (13.3%)	0
Vaginal trichomonas	2 (3.1%)	2 (3.1%)	0	0
Injury		**1 (1.5%)**		**1 (1.6%)**
Humerus fracture	0	1 (1.5%)	0	0
Periorbital hematoma		0		1 (1.6%)
Metabolism	**1 (1.5%)**	**1 (1.5%)**		
Hypoglycemia	0	1 (1.5%)	0	0
Hypokalemia	0	1 (1.5%)		
Increased appetite	1 (1.5%)	0		
Musculoskeletal	**1 (1.5%)**	**1 (1.5%)**	**1 (1.7%)**	**1 (1.6%)**
Back Pain	1 (1.5%)	1 (1.5%)	0	0
Muscle spasm	0	0	0	1 (1.6%)
Pain in Extremity	0	0	1 (1.7%)	0
Nervous System	**11 (16.9%)**	**4 (6.2%)**	**6 (10.0%)**	**11 (17.2%)**
Dizziness	0	1 (1.5%)	0	1 (1.6%)
Dysgeusia	0	0	0	1 (1.6%)
Headache	11 (16.9%)	3 (4.6%)	6 (10.0%)	6 (9.4%)
Migraine	0	0	1 (1.7%)	3 (4.7%)
Syncope	0	1 (1.5%)	0	0
Psychiatric	**1 (1.5%)**	**2 (3.1%)**	**1 (1.7%)**	
Anxiety	1 (1.5%)	0	0	
Attention Deficit	0	1 (1.5%)	0	0
Depression	0	0	1 (1.7%)	
Insomnia	0	1 (1.5%)	0	
Renal/Urinary	**1 (1.5%)**		**1 (1.7%)**	
Dysuria	0	0	1 (1.7%)	0
Pollakiuria	1 (1.5%)	0	0	
Reproductive	**8 (12.3%)**	**6 (9.2%)**	**6 (10.0%)**	**7 (10.9%)**

Dysmenorrhea	0	1 (1.5%)	1 (1.7%)	2 (3.1%)
Pelvic Pain	3 (4.6%)	1 (1.5%)	0	2 (3.1%)
Vaginal hemorrhage	0	0	2 (3.3%)	1 (1.6%)
Vaginal discharge	1 (1.5%)	0	1 (1.7%)	0
Vaginal odor	0	0	1 (1.7%)	0
VV burning	3 (4.6%)	2 (3.1%)	1 (1.7%)	1 (1.6%)
VV discomfort	1 (1.5%)	1 (1.5%)	0	1 (1.6%)
VV pain	0	0	0	1 (1.6%)
VV pruritus	1 (1.5%)	2 (3.1%)	4 (6.6%)	0
Respiratory/Thoracic	**3 (4.6%)**		**3 (5.0%)**	**1 (1.6%)**
Cough	1 (1.5%)		0	0
Nasal congestion	1 (1.5%)	0	1 (1.7%)	1 (1.6%)
Sinus congestion	1 (1.5%)		1 (1.7%)	0
Rhinitis	0		1 (1.7%)	0

The most common AEs included vaginal candidiasis, vulvo-vaginal symptoms (burning, discomfort and pruritus), pelvic pain and headache.

SAE

One Subject in the 1.3% x 1 day arm developed hypoglycemia. The subject was a 54 year old woman with history of insulin-dependent diabetes, schizophrenia and peripheral neuropathy. She was receiving Lantus and Humulin insulin, gabapentin, fluoxetine and bupropion. One week after receiving the study drug, she had a glucose of 41 associated with dizziness and syncope that led to fractured humerus. She was hospitalized for one day after which she left against medical advice. The SAE was assessed as unrelated to study drug.

Pregnancies

Three pregnancies were reported.
The first subject received 0.75% x 5 days. She had a negative pregnancy test on Study Day 1 and a positive test on Study Day 30 at the TOC visit. This subject had an abruptio placenta and premature labor at week 24 of gestation. She delivered a live baby weighing 570 gm with Apgar scores of 1 and 1 at 1 and 5 minutes. The baby died. Pathology revealed marked chorioamnionitis and subchorionitis.

The second subject received 1.3% x 5 days. She had a negative pregnancy test on Study Day 1 and a positive home pregnancy test on Day 17, confirmed at the study site. She had a spontaneous abortion at approximately 16 weeks gestation. No fetal abnormalities were noted.

The third subject received 0.75% x 5 days. She had a negative pregnancy test on Study Day 1, and a positive home pregnancy test on Day 15, confirmed at the study site. She completed her TOC visit on Day 22. Ten days later, an ultrasound revealed a 4.5 week sac, with no fetal pole, consistent with a blighted ovum. A dilation and curettage was performed.

Reviewer's Comments
Metronidazole is pregnancy category B. The narratives do not state whether the subjects who became pregnant still had BV or were cured. BV is associated with preterm labor and chorioamnionitis.

Phase 3 Placebo-Controlled Study - MP-1601-01

Study Design

This was a multicenter, randomized, double-blind study comparing the efficacy of metronidazole vaginal gel 1.3% single 5 gram dose versus vehicle in the treatment of BV. The study was conducted at 37 centers in the United States between May 31, 2012 and October 25, 2012.

Non-pregnant women at least 18 years of age and with a diagnosis of BV, defined as satisfying all of Amsel criteria, were enrolled. Women had to agree to abstain from intravaginal sexual activity for the first 7 days of the study and to use a non-lubricated condom for the remaining duration of the study.

Pregnant women, women menstruating at the time of diagnosis, women who had known or suspected other causes of vaginitis, who had received an antifungal or antimicrobial therapy within the previous 14 days, who had taken disulfiram, who had a history of hypersensitivity to metronidazole, who had an immunodeficiency, who were treated for cervical intra epithelial neoplasia or cervical carcinoma, who were using Coumadin or steroids, who had a clinically important medical event within the previous 30 days, or who were unable to abstain from alcohol for the initial 7 days of the study were excluded.

Pregnancy test, pelvic exam, Gram stain for Nugent score, rapid test for *T. vaginalis* antigen, wet mount (for clue cells, *T. vaginalis* and *Candida*) and nucleic acid test for *C. trachomatis* and *N. gonorrhoeae* were obtained at screening and at Day 21-30 (TOC visit). A Pap smear was obtained at screening if the subject did not have one documented within the past 12 months. Subjects were instructed to call the study investigator is symptoms did not improve within 3 to 4 days. Subjects returned for pelvic exam and evaluation on days 7 to 9, and were given a diary to record symptoms and a treatment satisfaction questionnaire. Pelvic exam was done on Days 21-30 (TOC/EOS visit). Nugent scoring was done by a microscopist unaware of the assigned treatment and confirmed by a second microscopist. In case of discordance, readings were performed by a third microscopist.

The primary efficacy endpoint was clinical cure at Day 21-30, defined as return of normal physiologic discharge as confirmed by the investigator with a negative whiff test and clue cells < 20%. Secondary endpoints were bacteriologic cure (Nugent score < 4) at Day 21 and Day 7, therapeutic cure (clinical plus bacteriologic cure) at Day 21 and Day 7

visit, clinical cure at Day 7 and resolution of symptoms as reported by the subject at Day 7. Testing for statistical significance of the secondary endpoints was conducted in a sequential manner.

Reviewer's Comments
The primary efficacy endpoint was recommended by the FDA. Previous BV studies, including the Phase 2 study GW05-0904, used therapeutic cure as the primary endpoint. In addition, the previous definition of clinical cure included pH criteria.

The MITT population included all randomized subjects who had negative tests for *N. gonorrhoeae* and *C. trachomatis* and had a Nugent score ≥4 at Visit 1. For the classification of clinical response, vaginal discharge was initially indicated as "present" or "absent" on the CRF. Because this response to this question was equivocal, the question was modified to a Yes or No answer to the question "has the original discharge characteristic of BV returned to a normal physiologic discharge?" The Primary Modified ITT population was defined as the subset of the MITT population who were evaluated on D 21 using the above yes or no question on the CRF. The PMITT population was the primary analysis population.

The PP population included subjects in the PMITT population who satisfied all the 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 during the study period, had no additional intravaginal products during the study period and had a TOC Gram stain Nugent score result obtained between days 21 and 30.

The safety population included all randomized subjects who applied any amount of study medication.

Using the PMITT population as the primary analysis population, 650 subjects needed to be randomized to attain power of 90% and a 2-sided alpha of 5%,.

Protocol Amendments

One amendment pertaining to the change in wording of the question regarding return of discharge to physiologic was implemented.

Subject Disposition

898 subjects were screened, and 651 were randomized, 325 to receive metronidazole gel and 326 to receive vehicle gel.

Table 21: Subject Disposition – Study MP-1601-01

	MVG 1.3%	Vehicle

Randomized	325	326
Completed Study	293 (90.2%)	288 (88.3%)
Discontinued	32 (9.8%)	38 (11.7%)
Reasons for Discontinuation		
Investigator Request	0	2 (0.6%)
Subject Request (no AE)	7 (2.2%)	12 (3.7%)
Lost to Follow up	10 (3.1%)	9 (23.7%)
GC or *Chlamydia*	8 (2.5%)	10 (2.8%)
Other	7 (2.2%)	5 (1.5%)
Withdrew consent	2	1
Did not use drug	0	1
Required further BV RX	4	3
Became Pregnant	1	0

Protocol Deviations

- 17 subjects used prohibited medications (9 in the metronidazole arm and 8 in the vehicle arm). One of these MVG subjects was included in the PP population because she was reported to be a clinical failure, the other 16 were excluded.
- 14 subjects (4 MVG and 10 vehicle) were dispensed but did not apply the study medication. These were excluded from the safety population.
- 4 subjects (1 MGV and 3 vehicle) applied the study medication > 2 days after randomization.
- Two subjects (both randomized to vehicle) had positive *Chlamydia* at baseline and were not discontinued.

Analysis Populations

The MITT, PMITT and PP populations included 292, 250 and 214 in the metronidazole arm, and 285, 237 and 204 in the vehicle arm.

Table 22: Analysis Populations – Study MP-1601-01

	MVG 1.3%	Vehicle
ITT	325	326
Excluded From MITT	33	41
GC or Chlamydia positive	9	13
Nugent not ≥ 4 Visit 1	24	28
MITT	292	285
Excluded From PMITT	75 (42+33)	89 (48+41)
Protocol change regarding Investigator question	42	48
PMITT	250	237
Excluded from PP	111 (36+75)	122 (33+89)
Did not apply study med within 2 days	5	13
Used prohibited meds	9	8
Did not have TOC Nugent	49	48
PP	214	204

Demographics

Table 23: Subject Demographics – Safety Population – Study MP-1601-01

	MVG 1.3% N = 326	Vehicle N = 325
Mean Age (SD)	32.2 (9.1)	34.6 (10.1)
Hispanic	48 (15.0%)	36 (11.4%)
Not Hispanic	278 (85.0%)	280 (88.6%)
Race		
White	126 (39.3%)	121 (38.3%)
Black	187 (58.3%)	188 (59.5%)
Other	8 (2.4%)	7 (2.2%)

Table 24: Subject Demographics – MITT – Study MP-1601-01

	MVG 1.3%) N = 292	Vehicle N = 285
Mean Age (SD)	32.1 (9.0)	34.7 (9.9)
Hispanic	44 (15.1%)	35 (12.3%)
Not Hispanic	248 (84.9%)	250 (87.7%)
Race		
White	112 (38.4%)	106 (37.2%)
Black	172 (58.9%)	173 (60.1%)
Other	8 (2.7%)	6 (2.8%)

Table 25: Subject Demographics – PMITT – Study MP-1601-01

	MVG 1.3% N = 250	Vehicle N = 237
Mean Age (SD)	32.2 (9.1)	34.6 (9.7)
Hispanic	36 (14.4%)	31 (13.1%)
Not Hispanic	214 (85.6%)	206 (86.9%)
Race		
White	94 (37.6%)	86 (36.3%)
Black	149 (59.6%)	146 (61.6%)
Other	7 (2.8%)	5 (2.1%)

Table 26: Subject Demographics – PP – Study MP-1601-01

	MVG 1.3% N = 214	Vehicle N = 204
Mean Age (SD)	32.1 (9.2)	34.5 (9.4)
Hispanic	32 (15.0%)	25 (12.3%)
Not Hispanic	182 (85.0%)	179 (87.7%)
Race		
White	79 (37.0%)	70 (34.3%)
Black	130 (60.7%)	129 (63.2%)
Other	5 (2.3%)	5 (2.5%)

Table 27: Baseline Disease Characteristics – PMITT – Study MP-1601-01

	MVG 1.3% N = 250	Vehicle N = 237
No BV in prior 12 months	172 (68.8%)	161 (67.9%)
VV itching		
Present	76 (30.4%)	76 (32.1%)
Absent	174 (69.6%)	161 (67.9%)
VV Irritation		
Present	88 (35.2%)	94 (39.7%)
Absent	162 (64.8%)	143 (60.3%)
VV Inflammation		
Present	79 (31.6%)	92 (38.8%)
Absent	171 (68.4%)	145 (61.2%)
Nugent Score		
Mean	8.5 (1.47)	8.4 (1.50)
Median	8	8

Reviewer's Comments
Subject's demographics were similar in both arms in the MITT, PMITT, PP and safety populations.

Site enrollment

No single site enrolled more than 10% of the subjects in either study arm in any of the analysis populations. In the MITT population, the sites that enrolled the highest number of subjects were sites 5, 11, 17 and 19 that respectively enrolled 21, 19, 20 and 21 subjects each in the metronidazole arm, and respectively enrolled 22, 19, 21 and 20 subjects in the vehicle arm.

Reviewer's Comments
Site inspection was not considered necessary for this application for the following reasons:

1- *No site enrolled more than 10% of the population,*
2- *Preliminary review of the efficacy analysis by site did not indicate that efficacy was driven by any site,*
3- *Metronidazole is not a new molecular entity and vaginal gel formulations are already approved and marketed, and*
4- *Several of the sites participating in this trial had been recently inspected by the FDA..*

Primary Efficacy Endpoint

The primary efficacy endpoint was clinical cure on Day 21-30 in the PMITT population. Metronidazole gel was superior to placebo in the MITT, PMITT and PP populations.

Table 28: Clinical Cure at Day 21 (TOC Visit) – Study MP-1601-01

PMITT				
	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH	P value
Clinical Cure (95% CI)	93 (37.2%) (31.2%, 43.5%)	63 (26.6%) (21.1%, 32.7%)	10.6% (2.4%, 18.8%)	0.010
MITT				
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Clinical Cure (95% CI)	108 (37.0%) (31.4%,42.8%)	76 (26.7%) (21.1%, 32.7%)	10.3% (2.8%, 17.9%)	0.007
PP				
	MVG 1.3% N = 214	Vehicle N = 204	Difference MVG-VEH	P value
Clinical Cure (95% CI)	87 (40.7%) (34.0%, 47.6%)	61 (29.9%) (23.7%, 36.7%)	10.8% (1.7%, 19.9%)	0.007

Secondary Endpoints

Table 29: Bacteriologic Cure – Day 21 – Study MP-1601-01

PMITT				
	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH	P value
Bacteriologic Cure (95% CI)	47 (18.8%) (14.2%, 24.2%)	19 (8.0%) (4.9%, 12.2%)	10.8% (4.8%, 16.7%)	< 0.001
MITT				
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Bacteriologic Cure (95% CI)	57 (19.5%) (15.1%, 24.5%)	22 (7.7%) (4.9%, 11.5%)	11.8% (6.3%, 17.3%)	< 0.001
PP				
	MVG 1.3% N = 214	Vehicle N = 204	Difference MVG-VEH	P value
Bacteriologic Cure (95% CI)	44 (20.6%) (15.1%, 26.0%)	14 (6.9%) (3.4%, 10.3%)	13.7% (7.0%, 20.4%)	< 0.001

Table 30: Therapeutic Cure – Day 21 (TOC Visit) - Study MP1601-01

PMITT				
	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH	P value
Therapeutic Cure (95% CI)	42 (16.8%) (12.4%, 22.0%)	17 (7.2%) (4.2%, 11.2%)	9.6% (3.9%, 15.3%)	< 0.001
MITT				
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Therapeutic Cure (95% CI)	49 (16.8%) (12.7%, 21.6%)	18 (6.3%) (3.8%, 9.8%)	10.5% (5.3%, 15.6%)	< 0.001

PP				
	MVG 1.3% N = 214	Vehicle N = 204	Difference MVG-VEH	P value
Therapeutic Cure (95% CI)	39 (18.2%) (13.1%, 23.4%)	15 (7.4%) (3.8%, 10.9%)	10.8% (4.7%, 16.9%)	< 0.001

Table 31: Bacteriologic Cure Day 7 – Study MP 1601-01

	Day 7 Analysis Population*			
	MVG 1.3% N = 202	Vehicle N = 205	Difference MVG-VEH	P value
Bacteriologic Cure (95% CI)	66 (32.7%) (26.3%, 39.6%)	13 (6.3%) (3.4%, 10.6%)	26.3% (19.1%, 33.6%)	< 0.001
	MITT			
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Bacteriologic Cure (95% CI)	99 (33.9%) (28.5%, 39.6%)	18 (6.3%) (3.8%, 9.8%)	27.6% (21.5%, 33.7%)	< 0.001

*Subjects in the PMITT who had their Day 7 vaginal discharge evaluated as a yes or no response to the "has the original discharge characteristic of BV returned to a normal physiologic discharge?"

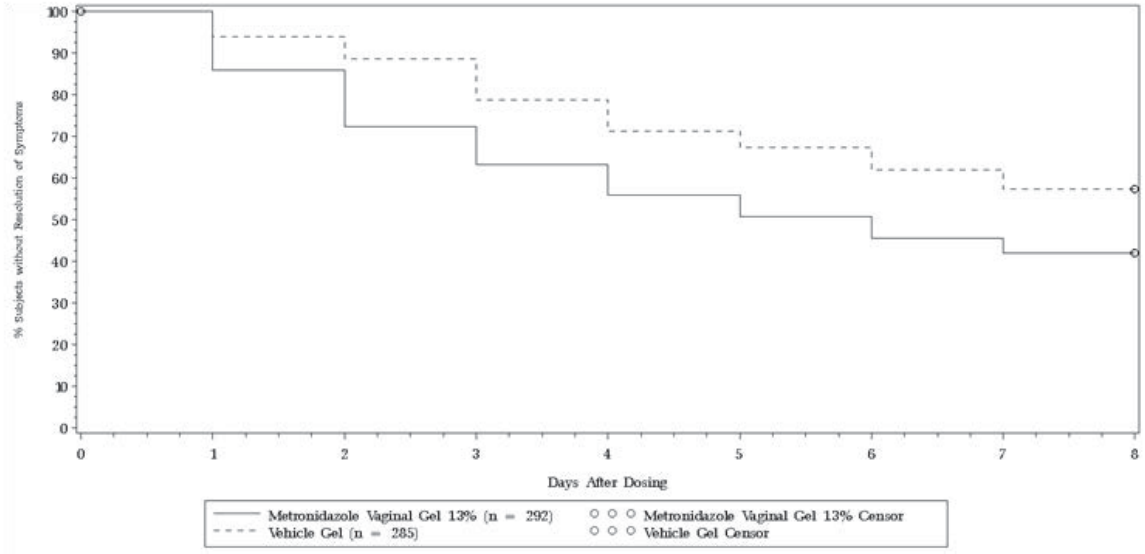
Table 32: Clinical Cure – Day 7 – Study MP 1601-01

	Day 7 Analysis Population			
	MVG 1.3% N = 202	Vehicle N = 205	Difference MVG-VEH	P value
Clinical Cure (95% CI)	93 (46.0%) (39.0%, 53.2%)	41 (20.0%) (14.8%, 26.1%)	26.0% (17.3%, 34.8%)	< 0.001
	MITT			
	MVG 1.3% N = 292	Vehicle N = 285	Difference MVG-VEH	P value
Clinical Cure (95% CI)	120 (41.1%) (35.4%, 47.0%)	57 (20.0%) (15.5%, 25.1%)	21.1% (13.8%, 28.4%)	< 0.001

Time to Resolution of Symptoms

The median time to resolution of symptoms as recorded in the subject's diary in the metronidazole gel arm was 6 days in the Day 7 and the MITT populations. Less than half of subjects in the vehicle group resolved their symptoms by Day 7; median time could not be calculated.

Figure 1: Kaplan- Meier Plot of Time to Resolution of Symptoms – Day 7 Analysis Population



The Kaplan-Meier plot for time to resolution of symptoms was similar for the Day 7, MITT and PMITT populations.

Subject Questionnaire

By Day 2, 42% and 24% of metronidazole and vehicle subjects respectively reported resolution of symptoms. Approximately 43% in each arm reported minimal leakage, and approximately 30% in each arm reported moderate leakage.

Subjects' responses to questions regarding satisfaction with the medication, relief of symptoms and amount of time it takes for symptoms to improve were scored. The mean score was significantly higher in the metronidazole gel arm compared to vehicle arm (69.9 +/- 24.9 vs. 54.9 +/-30.9, $p<0.001$).

Responses to questions regarding side effects, interference with physical activity or mental function were also scored. There were no differences between the treatment arms (mean score 96.1+/-12.6 vs. 96.3+/-13.2, $p=0.909$).

There was no difference rating the convenience of use of the single dose administration.

Clinical Cure in Subpopulations

Treatment Effect was similar in white and black subjects, and in subjects above or below the age of 35 years.

Table 33: Clinical Cure on Day 21 by Race – PMITT Population – MP 1601-01

Clinical Cure Day 21	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH
White	37/94 (39.4%)	26/86 (30.2%)	9.2%
Black or AA	54/149 (36.2%)	35/146 (24.0%)	12.2%
Other	2/7 (28.6%)	2/5 (40.0%)	-11.4%
Total	93/250 (37.2%)	63/237 (26.6%)	10.8%

Table 34: Clinical Cure Day 21 by Age – PMITT Population – MP-1601-01

Clinical Cure Day 21	MVG 1.3% N = 250	Vehicle N = 237	Difference MVG-VEH
< 35 years	57/162 (35.2%)	28/129 (21.7%)	13.5%
≥35 years	36/88 (40.1%)	35/108 (32.4%)	7.7%
Total	93/250 (37.2%)	63/237 (26.6%)	10.8%

Efficacy Conclusions
Metronidazole vaginal gel 1.3% was superior to vehicle for the primary endpoint of clinical cure at Day 21, and for the secondary endpoints of clinical cure at Day 7, bacteriologic cure at Days 7 and 21 and therapeutic cure at Day 21 in the MITT, PMITT and PP populations. Metronidazole gel resulted in more rapid resolution of symptoms and higher subject satisfaction. Age or race did not affect cure rates.

Safety Evaluation

Use of concomitant medications was similar in the two treatment arms, most commonly oral contraceptives and analgesics.

Adverse Events

In the metronidazole gel arm, 61 subjects (19.0%) experienced at least one AE. In the vehicle arm, 51 subjects (16.1%) experienced at least one AE. There were no deaths and no serious adverse events.

Table 35: Adverse Events – Study MP-1601-01

MedDRA v. 14.0	MVG 1.3% N = 321	Vehicle N = 316
Any AE	61 (19.0%)	51 (16.1%)
Blood and Lymphatic	**1 (0.3%)**	**0**
Anemia	1 (0.3%)	
Gastrointestinal	**15 (4.7%)**	**16 (5.1%)**
Abdominal discomfort	0	1 (0.3%)
Abdominal distension	1 (0.3%)	0
Abdominal Pain	3 (0.9%)	2 (0.6%)
Abdominal Pain Lower	0	1 (0.3%)
Abdominal Pain Upper	0	2 (0.6%)
Diarrhea	4 (1.2%)	5 (1.6%)
Dry Mouth	3 (0.9%)	1 (0.3%)

Nausea	5 (1.6%)	5 (1.6%)
Tooth impacted	1 (0.3%)	0
Toothache	1 (0.3%)	0
Vomiting	1 (0.3%)	0
General/Admin Site	2 (0.6%)	**1 (0.3%)**
Fatigue	1 (0.3%)	1 (0.3%)
Application site pain	1 (0.3%)	0
Abnormal taste	1 (0.3%)	0
Infection/Infestation	**26 (8.1%)**	**17 (5.4%)**
Cystitis	1 (0.3%)	0
Ear infection	1 (0.3%)	0
Folliculitis	1 (0.3%)	0
Infected Cyst	0	1 (0.3%)
Influenza	1 (0.3%)	0
Sinusitis	1 (0.3%)	0
Trichomoniasis	0	2 (0.6%)
URI	1 (0.3%)	1 (0.3%)
Viral infection	0	1 (0.3%)
Vulval abscess	1 (0.3%)	0
VVC	18 (5.6%)	10 (3.2%)
Nasopharyngitis	0 (0.3%)	2 (0.6%)
Injury	**1 (0.3%)**	**0**
Ankle Contusion	1 (0.3%)	
Musculoskeletal	**2 (0.6%)**	**2 (0.6%)**
Back Pain	1 (0.3%)	1(0.3%)
Extremity Pain	0	1 (0.3%)
Neck Pain	1 (0.3%)	0
Nervous System	**8 (2.5%)**	**4 (1.3%)**
Dizziness	1 (0.3%)	0
Headache	7 (2.2%)	4 (1.3%)
Psychiatric	**2 (0.6%)**	
Anxiety	2 (0.6%)	**0**
ETOH withdrawal	1 (0.3%)	
Renal	**1 (0.3%)**	**2 (0.6%)**
Dysuria	0	1 (0.3%)
Pollkiuria	1 (0.3%)	1 (0.3%)
Reproductive/Urinary	**17 (5.3%)**	**16 (5.1%)**
Breast pain	1 (0.3%)	0
Cervical dysplasia	1 (0.3%)	0
Dysmenorrhea	4 (1.2%)	1 (0.3%)
Dyspareunia	0	1 (0.3%)
Metorrhagia	0	2 (0.6%)
Pelvic discomfort	1 (0.3%)	1 (0.3%)
Pelvic pain	2 (0.6%)	2 (0.6%)
Uterine spasm	0	1 (0.3%)
Vaginismus	0	1 (0.3%)
Vaginal hemorrhage	3 (0.9%)	0
VV burning	3 (0.9%)	2 (0.6%)
VV discomfort	1 (0.3%)	1 (0.3%)

VV Dryness	0	1 (0.3%)
VV pruritus	5 (1.6%)	5 (1.6%)
Respiratory/Thoracic	**1 (0.3%)**	**1 (0.3%)**
Cough	0	1 (0.3%)
Sinus congestion	1 (0.3%)	0
Skin/SC	**1 (0.3%)**	**0**
Urticaria	1 (0.3%)	
Vascular	**1 (0.3%)**	**0**
Hypertension	1 (0.3%)	

Adverse events that occurred in ≥1% of subjects in either arm included diarrhea, nausea, headache, dysmenorrhea, vulvo-vaginal candidiasis (VVC) and vulvo-vaginal pruritus. AEs that occurred more frequently in the metronidazole gel arm were VVC, VV pruritus, vaginal hemorrhage and dysmenorrhea.

Pregnancy

Three subjects became pregnant during the study, one in the metronidazole gel arm and two in the vehicle gel arm. The subject in the metronidazole gel arm was discontinued from the study due to a positive pregnancy test on Day 11. Both vehicle subjects completed the study on Day 21 at which time the pregnancy test was positive. Pregnancy outcome was known for one of the vehicle subjects. She delivered at 36 weeks with reported oligohydramnios with fetal deceleration. No birth defects or anomalies were noted in the baby.

Reviewer's Comments
Product labeling for metronidazole vaginal gel 0.75% formulations lists the following AEs as occurring in ≥ 1% of patients in clinical studies: headache, pruritus, (b) (4), (b) (4), nausea, (b) (4), rash, (b) (4), diarrhea, (b) (4) and (b) (4). The AE profile noted in this Phase 3 study is similar.

Integrated Efficacy

The dose-ranging Phase 2 studies and the Phase 3 study used different primary efficacy endpoints. In addition, the definition of clinical cure did not incorporate pH criteria in the pivotal Phase 3 Study. The results of the two studies will not be integrated.

Metronidazole vaginal gel 1.3% was superior to placebo for the primary endpoint of clinical cure at Day 21 in all the analysis populations (MITT, PMITT, and PP). Metronidazole vaginal gel 1.3% also resulted in faster time to symptom resolution and in higher subject satisfaction compared to vehicle only.

Integrated Safety

Safety results will be presented for all BV subjects who received any dose of 1.3% gel and compared to subjects who received 0.75% gel and subjects who received vehicle. 189 subjects received at least one dose of metronidazole gel 1.3% in Study GW05-0904 and 321 received a dose in Study MP 1601-01 (total 510 subjects). 65 subjects received 0.75% gel in Study GW05-0904 and 321 subjects received vehicle.

Table 36: Adverse Events Occurring in ≥1% of BV Subjects who Received Metronidazole Gel 1.3%, 0.75% or Vehicle – Studies MP 1601-01 and GW05-0904

MedDRA v. 14.0	Any MVG 1.3% N = 510	MVG 0.75% N = 65	Vehicle N = 316
Any AE	125 (24.5%)	28 (43.1%)	51 (16.1%)
Gastrointestinal	**28 (5.5%)**	**3 (4.6%)**	**16 (5.1%)**
Abdominal Pain	9 (1.8%)	0	2 (0.6%)
Diarrhea	5 (1.0%)	0	5 (1.6%)
Nausea	10 (2.0%)	0	5 (1.6%)
Infection/Infestation	**40 (7.8%)**	**14 (21.5%)**	**17 (5.4%)**
Trichomoniasis	0	2 (3.1%)	2 (0.6%)
UTI	2 (0.4%)	2 (3.1%)	0
VVC	34 (6.7%)	9 (13.8%)	10 (3.2%)
Nasopharyngitis	7 (1.4%)	1 (1.5%)	2 (0.6%)
Nervous System	**29 (5.7%)**	**11 (16.9%)**	**4 (1.3%)**
Headache	22 (4.3%)	11 (16.9%)	4 (1.3%)
Reproductive/Urinary	**17 (3.3%)**	**8 (12.3%)**	**16 (5.1%)**
Dysmenorrhea	8 (1.6%)	0	1 (0.3%)
Pelvic pain	3 (0.6%)	3 (4.6%)	2 (0.6%)
VV burning	7 (1.4%)	3 (4.6%)	2 (0.6%)
VV pruritus	11 (2.2%)	1 (1.5%)	5 (1.6%)

Adverse Events noted in ≥1% of subjects who received any regimen of metronidazole gel 1.3% included abdominal pain, diarrhea, nausea, VVC, nasopharyngitis, headache, dysmehorrhea, vulvo-vaginal burning and vulvo-vaginal pruritus. Adverse Events noted more frequently in the 1.3% gel recipients compared to vehicle recipients included abdominal pain, headache, VVC, nasopharyngitis, dysmenorrhea, vulvo-vaginal burning and vulvo-vaginal pruritus.

Pediatric Development Plan

The sponsor requested waiver of pediatric studies in pre-menarchal females because the low incidence and prevalence of BV in this population renders the studies unfeasible. This request was discussed with the Pediatric Review Committee on December 4, 2013. PeRC granted a waiver from PREA required studies for females less than the age of 12 years.

For products approved for the treatment of BV, labeling states that effectiveness in post-menarchal females < 18 years of age can be extrapolated from adult studies. (b) (4)

(b) (4). On November 8, 2013, DAIP indicated to the sponsor that a study to evaluate the safety and tolerability of metronidazole gel 1.3% in the adolescent population is required. In response, the sponsor proposed a clinical (b) (4) (b) (4) study comparing metronidazole vaginal gel 1.3% single dose to vehicle gel (b) (4) < 18 years of age. (b) (4) . This proposal was discussed with PeRC on December 4, 2013. PeRC agreed to grant a deferral of PREA required studies in females 12 -<18 years of age.

Labeling Recommendations

Labeling will be similar to metronidazole gel 0.75% with the exception of section 8.4: the statement " (b) (4) will be replaced by the statement that safety and efficacy in pediatric patients below the age of 18 have not been established.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HALA H SHAMSUDDIN
01/14/2014

THOMAS D SMITH
01/15/2014

NDA/BLA Number: 205-223 SN 000 **Applicant: Valeant Pharmaceuticals LLC** **Stamp Date: May 24, 2013**

Drug Name: Metronidazole vaginal gel 1.3% **NDA/BLA Type: 505(b)1**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: GW05-0904 Sample Size: 289 Arms: metro gel 1.3% for one day, three days or five days vs. metro gel 0.75% for 5 days Location in submission: M5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			The Division agreed that a single Phase 3 study and supporting

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 MP-1601-01 Indication: Treatment of BV				evidence from Phase 2 study and/or studies of other doses or formulations can support this NDA application. The sponsor is cross-referencing NDA 20-208 metro gel 0.75%
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Studies were conducted in the United States
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	The product is for local application with minimal systemic absorption
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary used for mapping investigator verbatim terms to preferred terms?	X			MedDRA version 14.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			

	Content Parameter	Yes	No	NA	Comment
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor is requesting a waiver for pediatric patients who have not experienced menarche
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Hala Shamsuddin MD — June 3, 2013

Reviewing Medical Officer — Date

Thomas Smith MD

Clinical Team Leader — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HALA H SHAMSUDDIN
07/16/2013

THOMAS D SMITH
07/16/2013