

Clinical Review
Caroline J. Jjingo
NDA 205,223
Metronidazole Vaginal Gel 1.3%/Nuvessa™

CLINICAL REVIEW

Application Type	Pediatric Efficacy Supplement
Application Number	NDA 205,223; S-002
Priority or Standard	Priority
Submit Date	February 5, 2018
Received Date	February 5, 2015
PDUFA Goal Date	August 5, 2018
Division/Office	Division of Anti-Infective Products (DAIP)
Reviewer Name	Caroline J. Jjingo, MD, MPH
Review Completion Date	June 11, 2018
Established/Proper Name	Metronidazole Vaginal Gel 1.3%
(Proposed) Trade Name	Nuvessa™
Applicant	Chemo Research SL
Dosage Form	Vaginal gel (1.3%) containing 65-mg of metronidazole in 5 grams of gel in a pre-filled applicator
Applicant Proposed Dosing Regimen	A single-dose, pre-filled disposable applicator administered once intravaginally at bedtime
Applicant Proposed Indication/Population	Treatment of bacterial vaginosis (BV) in non-pregnant women and adolescents ages 12 to <18 years old
Recommendation on Regulatory Action	Approval
Recommended Indication/Population (if applicable)	Treatment of BV in non-pregnant women and adolescents ages 12 to <18 years old

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BV	bacterial vaginosis
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	cure rate
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GCP	good clinical practice
GI	gastrointestinal
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
PeRC	Pediatric Review Committee
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMITT	primary modified intent to treat
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PT	preferred terms
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

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SOC	system organ classification
sNDA	supplemental NDA
TEAE	treatment emergent adverse event
TOC	test of cure
VVC	vulvovaginal candidiasis

1. Executive Summary

1.1. Product Introduction

Nuvessa™ (metronidazole vaginal gel 1.3%) is a nitroimidazole antimicrobial currently indicated for the treatment of bacterial vaginosis (BV) in non-pregnant adult women ages ≥ 18 years old.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The evidence provided in this supplemental NDA (sNDA) indicates that when administered to non-pregnant pediatric patients between the ages of 12 and <18 years old who are diagnosed with BV, metronidazole vaginal gel 1.3% (Nuvessa™) has a safety profile comparable to that of non-pregnant adult women. Nuvessa was approved in March 2014, with a Pediatric Research Equity Act (PREA) postmarket requirement (PMR), PMR 2123-001, to determine Nuvessa's safety and tolerability in postmenarcheal, adolescent females. Study MG-1401 was conducted in fulfillment of PMR 2123-001. The study was not powered to determine efficacy. Efficacy was extrapolated from findings in adult women ages 18 years old and older.

This reviewer concludes that, based on the submitted evidence, the Applicant has provided adequate information in support of Nuvessa's safety and tolerability in pediatric patients 12 to <18 years old.

2. Therapeutic Context

2.1. Analysis of Condition

BV affects 8-23% of all women of reproductive age and remains the most common of vaginal infections in this demographic. Approximately 60% of all cases of BV are symptomatic, and are often characterized by increased amounts of malodorous vaginal discharge. Gram-negative anaerobes, which are implicated in the pathogenesis of BV, secrete mucin-degrading enzymes which cause abnormal vaginal discharge resulting in the degradation of normal vaginal mucin gel. The "fishy" odor associated with BV results from the volatilization of amines produced by the metabolism of anaerobic bacteria.

BV results in an imbalance of hydrogen peroxide-producing *Lactobacillus* species due to overgrowth of such commensal anaerobes as *Gardnerella vaginalis*, *Prevotella* species, anaerobic Gram-positive cocci, *Mobiluncus* species, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. BV rapidly responds to antibiotic treatment; however, BV is characterized by high rates of early recurrence (30% at 3 months, 50% at 6 months) which may reflect early relapse or more likely late reinfection.

2.2. Analysis of Current Treatment Options

Current FDA Approved Treatment Options for bacterial vaginosis are found in **Table 1**.

Table 1: FDA Approved Treatments for Bacterial Vaginosis

Drug	Route of Administration	Pediatric Dosing Age Cohorts	Indications	Pediatric Dosing
Clindamycin hydrochloride capsules, USP	Oral	No	Anaerobic infections of the female pelvis and genital tract (does not specifically state BV)	Pediatric: Not Available
Clindamycin Phosphate Vaginal Cream USP, 2%	Intravaginal	No	Treatment of bacterial vaginosis	Pediatric: Not Available
Clindamycin Phosphate Vaginal Suppositories (Cleocin® Vaginal Ovules)	Intravaginal	No	Treatment of bacterial vaginosis in non-pregnant, adult women	Pediatric: Not Available
Metronidazole Vaginal gel 0.75% (MetroGel-Vaginal)	Intravaginal	No	Treatment of bacterial vaginosis	Pediatric: Not Available
Secnidazole oral granules	Once Orally	No	Treatment of bacterial vaginosis in adult women	Pediatric: Not Available
Tinidazole	Oral	No	Treatment of bacterial vaginosis in non-pregnant, adult women	Pediatric: Not Available

Although not FDA approved for the treatment of BV, Centers for Disease Control (CDC) recommends clindamycin 300 mg orally twice daily x 7 days and metronidazole 500-mg administered twice daily x 7 days for this treatment indication.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nuvessa™ (metronidazole vaginal gel 1.3%) was approved by FDA in March 2014 for the treatment of bacterial vaginosis in non-pregnant adult women ages ≥ 18 years and older. According to the Applicant's 2017-2018 Annual Report, (b)(4).

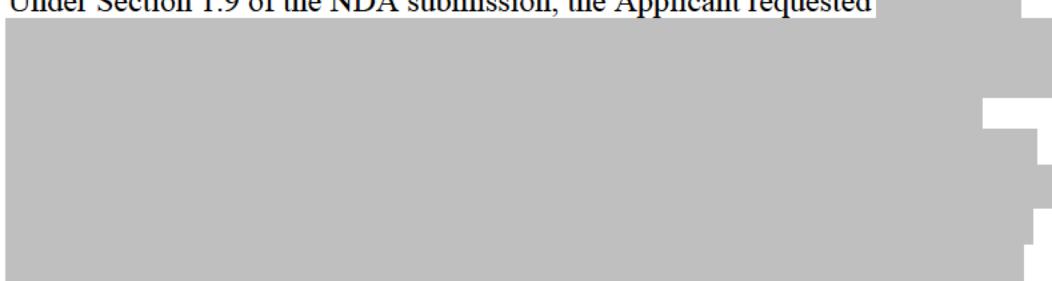
3.2. Summary of Presubmission Regulatory Activity Related to Submission

Key dates in Nuvessa's U.S. pediatric clinical development regulatory history are summarized below.

24 May 2013: Valeant Pharmaceuticals North American LLC ("Valeant") submitted to the Division an original NDA for metronidazole vaginal gel 1.3% for the "topical treatment of bacterial vaginosis in non-pregnant women". The clinical study program supporting this NDA was conducted under IND 107,484.

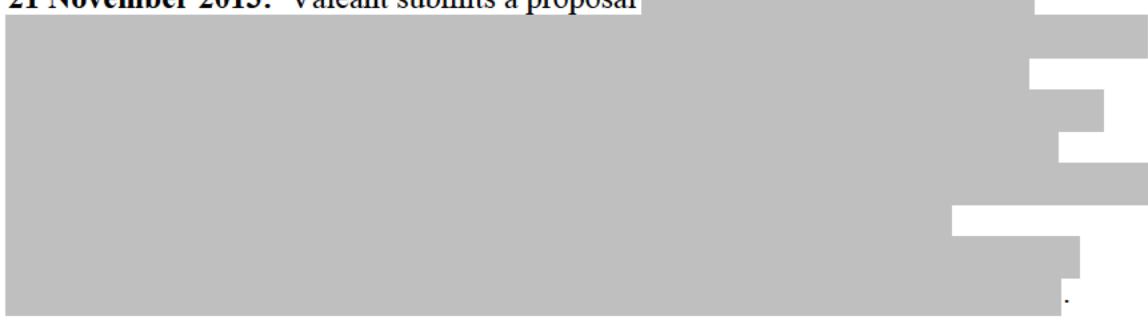
- Under Section 1.9 of the NDA submission, the Applicant requested

(b) (4)



21 November 2013: Valeant submits a proposal

(b) (4)



4 December 2013: The Pediatric Review Committee (PeRC) agreed with the Division to grant a partial waiver to study Nuvessa in patients < 12 years of age because studies would be impossible or highly impractical to conduct in this age group. The PeRC noted that the standard age used to define patients who are postmenarcheal for other products (e.g., oral contraceptive products) is 12 years of age and above. A pediatric deferral would apply to patients 12 to 17 years of age. The Applicant was to fulfill PMR 2123-01 by conducting "A clinical trial to evaluate the safety of metronidazole gel 1.3% single dose in the treatment of bacterial vaginosis in females 12-<18 years of age." The anticipated final protocol submission date was to be June 2014 and the final study report submission date was to be June 2015. This PMR was required under PREA to evaluate the safety of metronidazole vaginal gel 1.3% in adolescent females since safety data was lacking in this sub-population. Previous drugs approved for the treatment of BV had extrapolated efficacy and safety from adults.

24 March 2014: NDA 205,223, for Nuvessa (metronidazole vaginal gel 1.3%) was approved for the treatment of bacterial vaginosis in non-pregnant women ages 18 and

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older. Nuvessa was approved with PMR 2123-01 to conduct “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.” The anticipated completion date for the PMR study was December 2015 and the final protocol submission date was planned for June 2016.

1 July 2014: Transfer of ownership of NDA 205,223 went from Valeant to Watson Laboratories Inc. (Watson).

25 July 2014: Under IND 107,484, Watson submitted the final protocol for PMR 2123-001 (which was renamed Study MG1401) entitled “A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Metronidazole Vaginal Gel 1.3% in Adolescent Female Subjects with Bacterial Vaginosis.” Citing ethical concerns in issuing placebo to subjects randomized to placebo (4:1 active: placebo), the new Applicant proposed conducting an open-label, non-placebo controlled study also with 60 subjects.

29 September 2015: The Applicant, now Actavis Laboratories UT, Inc. requested a deferral extension of PMR 2123-01, citing recruitment challenges preventing them from achieving the originally anticipated study completion date of December 2015. The foremost challenges were: a lack of prospective recruitment sites interested in participation; low numbers of adolescent subjects with BV; prospective subjects’ unwillingness to delay BV treatment in order to obtain parental consent prior to study drug administration; and parental unwillingness or inability to be present for study visits. They proposed extending the study completion date from December 2015 to December 2017 and delaying the final report submission date from June 2016 to June 2018.

4 November 2015: The PeRC agreed to a second deferral extension after determining that the Applicant had demonstrated good faith attempts to increase enrollment and the Division agreed that there were considerable difficulties in obtaining parental consent to conduct the trial. The PeRC also permitted the Applicant time to increase enrollment by implementing novel informed consent methods.

13 November 2015: The Division agreed to the Applicant’s deferral extension request for PREA PMR 2123-001 because of delays in subject recruitment and site involvement.

19 December 2017: The Applicant, now Chemo Research SL, submitted the final Clinical Study Report MG-1401.

3.3. Foreign Regulatory Actions and Marketing History

According to the Applicant, [REDACTED] (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

As this was a safety and tolerability study, there were no significant issues pertaining to other review disciplines.

5. Sources of Clinical Data and Review Strategy

5.1. Review Strategy

This review of safety in pediatric patients is based upon the evaluation of safety data provided by the Applicant in their clinical study report (CSR) and accompanying data listings/tables pertaining to a single open-label, multicenter study (Study MG 1401) conducted at 5 U.S. sites.

Efficacy was extrapolated from findings in adults because the pathophysiology of BV and the response to therapy are similar in adolescents and adults.

6. Review of Relevant Individual Trials Used to Support Safety/Efficacy

6.1. Study MG1401

Study MG1401 entitled “A Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Metronidazole Vaginal Gel 1.3% in Adolescent Female Subjects with Bacterial Vaginosis (BV)” was a multicenter, open-label study conducted in fulfillment of PMR 2123-001 to assess the safety and tolerability of metronidazole vaginal gel 1.3% administered via a single dose applicator to postmenarcheal, adolescent females between the ages of 12 and <18 years old with a confirmed diagnosis of BV. The study was conducted, from 12 August 2015 to 5 October 2016, in 5 U.S. centers.

Prospective subjects were eligible for study inclusion if they met the following criteria: were ages 12 to <18 years old, provided written assent and parental/legal guardian informed consent (when applicable), had a negative urine pregnancy, and demonstrated *all* of the following pre-requisite criteria for a clinical diagnosis of BV (Amsel’s criteria):

- Off-white (milky or gray), thin, homogeneous discharge
- The presence of “clue cells” $\geq 20\%$ of the total epithelial cells on microscopic examination of the saline “wet mount”
- pH of vaginal fluid ≥ 4.7
- A positive 10% KOH “whiff test”

Prospective subjects were *ineligible* for study participation if they demonstrated any of the following **key** characteristics:

- Were pregnant, lactating, or planning to become pregnant during the study period
- Were currently menstruating or anticipated the onset of menses during the first 9 days of the study
- Had evidence of other infectious causes of vulvovaginitis such as candidiasis and/or *Trichomonas vaginalis* or any other vulvovaginal infection or condition that, in the investigator's opinion, would have confounded the interpretation of the results of the study
- Had severe symptoms of dysuria and/or pruritus, burning, or irritation, in the vulvovaginal area
- Had received systemic or intravaginal antifungal, antibacterial or antiparasitic drugs within 14 days of Screening/Baseline Visit on Day 1. Antiviral therapies (non-intravaginal) were acceptable
- Had taken disulfiram or systemic corticosteroids (oral or injected) within 14 days of Screening/Baseline Visit on Day 1
- Had sexual intravaginal intercourse within 24 hours of the Screening/Baseline Visit on Day 1

The study was divided into two periods: a Screening/Treatment Period (Day 1) and a Follow-Up Period (Days 2 to 7 [\pm 2 days] and a Safety Visit on Day 8 [\pm 2 days]). The Screening/Treatment Period included: an evaluation for study eligibility; a vaginal examination and collection of a vaginal fluid specimen for such microorganisms as *Trichomonas vaginalis*, *Candida*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*; and self-administration of Nuvessa at bedtime on Day 1. The Follow-Up Period consisted of telephone contact with a staff member on Study Day 2 and a Safety Visit on Study Day 8 (\pm 2 days) which notably included a review of adverse events (AEs), a vaginal examination and a vaginal tolerability evaluation for the presence and severity of vulvovaginal itching and irritation (subject description) and vaginal inflammation (investigator-assessed). All enrolled subjects who self administered Nuvessa were required to complete a daily diary where they assessed vaginal discharge and vaginal odor from Day 1 through the night prior to the Safety Visit on Day 8.

The primary analysis, the evaluation of safety in the safety population, included an assessment of treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities (MedDRA) system organ classifications (SOC) and preferred terms (PTs); test article compliance; vital signs; vaginal examination and vaginal tolerability. The safety population included "all subjects in the enrolled population who self-administered Nuvessa."

A secondary objective of the study was each subject's assessment of the presence or absence of vaginal discharge and/or odor as recorded in a daily diary (the efficacy endpoint), as assessed in the per-protocol (PP) population, defined as "all subjects in the Safety population who completed the study and did not have any major protocol

violations.” This endpoint was not powered to determine efficacy in the adolescent sub-population, but rather efficacy was to be extrapolated from the adult population since the disease pathology of BV is not different between adult and adolescent women. Efficacy was extrapolated from adult Phase 3 registrational trials.

Medical Reviewer’s Comments

The study design, eligibility criteria, and safety assessments are deemed appropriate.

6.1.2. Study Results

Patient Disposition

In all, a total of 65 adolescent females were screened for study eligibility, 5 (7.7%) of whom were assessed as “screen failures” for failure to meet certain eligibility criteria. Of the 60 enrollees, 58 (96.7%) completed the study and 2 (3.3%) were lost to follow-up.

Medical Reviewer’s Comments

Subject retention for this study was good with 58 (96.7%) of enrollees self-administering study drug and comprising the per protocol population. All 60 subjects were included in the safety population.

Protocol Deviations

No protocol deviations that affected the statistical analysis were reported by the Applicant.

Compliance

Study compliance was good with 59 (98.3%) of 60 subjects administering a single dose of Nuvessa on Study Day 1 and 1 (1.7%) subject administering the drug the day after screening. All 58 (100%) subjects comprising the per protocol population completed diary entries for Study Days 1 through 5, while 55, 51, 18, and 11 subjects on Study Days 6, 7, 8 and 8 (+1 Day) completed diary entries as expected. Only 1 of the 9 subjects expected to complete a diary entry on Study Day 8 (+2) failed to do so.

Medical Reviewer’s Comments

As described above, subject compliance with both the one time single dose administration of Nuvessa as well as with the daily diary entries was either 100% or close to 100%.

7. Integrated Review of Efficacy

7.1. Primary Efficacy Endpoint

While this study was primarily conducted to assess the safety and tolerability of Nuvessa in adolescents 12 to <18 years of age, the primary efficacy endpoint was to assess for the presence or absence of daily, self-reported vaginal discharge and/or odor in each subject

comprising the per protocol population as recorded in their daily diaries. Results of the efficacy endpoint can be found below in **Table 2**.

Table 2 Results of Primary Efficacy Endpoint

Diary Entry Time Point	Vaginal Discharge and Odor Symptoms	Per Protocol Population Total (N=58) n/N1 (%)
Day 1	No symptoms	3/58 (5.2)
	Discharge only/No odor	14/58 (24.1)
	Odor only/No discharge	1/58 (1.7)
	Both discharge and odor	40/58 (69.0)
Day 6	No symptoms	38/58 (65.5)
	Discharge only/No odor	16/58 (27.6)
	Odor only/No discharge	2/58 (3.4)
	Both discharge and odor	2/58 (3.4)

Source: Adapted from Table 11-1 of the Clinical Study Report and Statistical Review by Dr. Cheryl Dixon (statistical reviewer)

Notes: Day 1 was the day the subject administered the test article (i.e., the subject self-assessment of vaginal discharge and odor symptoms prior to dosing). Post dose time points were subject self-assessments of vaginal discharge and odor symptoms for diary entries on or after Day 2.

N1= the number of subjects in the PP population with an available response to vaginal discharge and odor symptoms at the indicated diary entry time point. One subject (Subject (b) (6)) administered the test article one day after the screening/baseline visit.

Medical Reviewer's Comments

Following single dose administration of Nuvessa, 66% (38/58) of all subjects self-reported no symptoms (absence of both vaginal discharge and odor) by Study Day 6. In comparison, MP-1601-01, the Phase 3 randomized, multicenter, double-blind registrational trial evaluating the safety and efficacy of a single intravaginal dose of metronidazole vaginal gel 1.3% versus a single intravaginal dose of vehicle gel in adult women with BV, had cure rates of 37.2% in subjects receiving metronidazole vaginal gel 1.3% versus 26.6% in subjects receiving vehicle gel, with a statistically significant difference of 10.6% (P-value= 0.010). The primary analysis was observed cure rate (CR) at test of cure (TOC, Day 21 to 30).

Briefly, MP-1601-01, enrolled 651 women ages \geq 18 years old. The primary efficacy analysis was assessed in the primary modified intention to treat (PMITT) population, defined as the subset of subjects in the MITT population evaluated on Day 21 who responded to a questionnaire inquiring on the presence or absence of vaginal discharge. It was comprised of 250 women in the metronidazole vaginal gel arm and 237 women in the vehicle gel arm. The primary efficacy endpoint was clinical cure, defined as a return to normal physiological discharge as confirmed by the investigator by a negative whiff test and clue cells <20%, at test of cure (TOC, Day 21 to 30). Secondary efficacy

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endpoints included bacteriological cure and therapeutic cure. Eighty-nine percent of all subjects completed the study.

8. Review of Safety

8.1. Safety Review Approach

The safety population was comprised of all individuals who self-administered a single dose of Nuvessa, in this case all 60 enrolled subjects. In her assessment of safety data, the clinical reviewer conducted a thorough review of the data contained in the CSR and in the accompanying data listings and tables provided by the Applicant.

8.2. Review of Safety Database

8.2.1. Overall Exposure

Table 3 below summarizes the study's analysis populations as described in Section 6.1.2 Study Results.

Table 3 Study Analysis Populations

Data Set	Subject Total N
Screened Population	65
Enrolled Population	60
Safety Population	60
Per Protocol Population	58

Source: Adapted from Table 14.1.1

8.2.2. Relevant Characteristics of the Safety Population

Table 4 provides an overview of relevant subject characteristics.

Table 4 Subject Demographics, Safety Population

Characteristic	Subject Total N=60 n (%)
Age (years)	
Mean (SD)	15.3 (1.4)
Median (min, max)	15.5 (12,17)
Sex, n (%)	
Female	60 (100.0)
Race, n (%)	

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Characteristic	Subject Total N=60 n (%)
Black/African-American, non-Hispanic	28 (46.7)
Caucasian/White, non-Hispanic	7 (11.7)
Black, Hispanic	1 (1.6)
White, Hispanic	20 (33.3)
Asian/Asian-American	0 (0.0)
Native American/Alaska Native	0 (0.0)
Native Hawaiian/Pacific Islander	2 (3.3)
Multi-Racial	2 (3.3)
Ethnicity, n (%)	
Hispanic/Latina	21 (35.0)
Non-Hispanic/Non-Latina	39 (65.0)
Weight (kg)	
Mean (SD)	65.3 (16.7)
Median (min, max)	60.2 (44.0, 126.6)
Height (cm)	
Mean (SD)	159.9 (7.2)
Median (min, max)	160.0 (132.1, 175.3)
BMI (kg/m²)	
Mean (SD)	25.6 (6.4)
Median (min, max)	24.0 (17.2, 43.4)
Vaginal fluid pH	
Mean (SD)	5.54 (0.50)
Median (min, max)	5.50 (4.7, 7.0)
Source: Table 10-3 of Clinical Study Report	
Abbreviations: BMI= body mass index; Max= maximum; Min= minimum	

Medical Reviewer's Comments

There were a total of 5 enrolling sites from which the safety population was recruited. A single site, Site 318 enrolled 42 (70.0%; 42/60) of all enrolled subjects; whereas the remaining 4 sites enrolled all other subjects (30.0%; 18/60).

The safety population was comprised of 60 adolescents with black, non-Hispanic and white, Hispanic adolescents, accounting for 46.7% and 33.3% of all participants, respectively. Approximately 18% of all other participants were either non-Hispanic, white; Hawaiian, native; or bi-racial. The mean age of participants was 15.3 years, with

5% (3 of 60), 10% (6 of 60) and 12% (7 of 60) of all participants ages 12, 13 and 14 years old, respectively. The mean BMI of enrolled subjects was 25.6.

Consistent with eligibility criteria, all subjects had a positive KOH whiff test and had ≥20% clue cells. Mean vaginal fluid pH was 5.5. During the Screening Visit, a total of 6 (10.0%) subjects tested positive for chlamydia. 86.7% (52/60) and 98.3% (58/60) of subjects, respectively, were tested for trichomonas or N. gonorrhoeae, and all were found to be negative. Three (5.0%) subjects reported having had a previous episode of BV several months prior to study enrollment for which they were treated with metronidazole, and 1 subject each indicated having a history of vaginitis (not otherwise specified) or Gardnerella (ongoing) (Listing 16.2.3.2 Medical/Surgical and Vaginosis History).

The most frequently cited class of concomitant medications was birth control with 6 of 60 (10.0%) subjects reporting being either on an oral, intramuscular or transdermal contraceptive. Four (6.7%) subjects were treated concomitantly with either doxycycline or azithromycin for chlamydial infections.

8.4 Safety Results

8.4.1. Deaths

No subjects died during the study.

8.4.2. Serious Adverse Events

A single subject, a 15 year old female with a documented suicide attempt, sustained the sole Serious Adverse Event (SAE) to occur in this study. This event was deemed by the Applicant to be unrelated to the drug product.

Medical Reviewer's Comment

There is no reason to suspect that the suicide attempt by ingestion of paroxetine and pseudoephedrine tablets and inhalation of alprazolam tablets was related to study treatment. The subject in question had a history of anxiety and depression. The event occurred on Study Day 19, 18 days after the subject self-administered the single dose of study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no subjects who either discontinued the study treatment or dropped out of the study due to an adverse event.

8.4.4. Significant Adverse Events

There were no reported significant adverse events that occurred during the course of the study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A total of 6 (10%) of the 60 subjects in the safety population experienced *at least* one treatment emergent adverse reaction/event (TEAE). Altogether these six subjects reported a total of 9 treatment emergent adverse events, most of which were assessed by the Applicant as being unrelated to the study drug (88.9%; 8 of 9) and of mild intensity (88.9%; 8 of 9). Please see **Table 5** below for further details.

Table 5 Subjects with at Least One Treatment Emergent Adverse Event (TEAE), Safety Population

Body System	Adverse Reaction	Subject Total (N=60) n (%)
Subjects with at least 1 TEAE		6 (10.0)
Gastrointestinal Disorders	Constipation ^a	1 (1.7)
	Nausea ^a	1 (1.7)
	Vomiting ^a	1 (1.7)
Infections and Infestations	Chlamydia Infection	1 (1.7)
	Nasopharyngitis	1 (1.7)
Musculoskeletal and Connective Tissue Disorders	Back Pain ^a	2 (3.3)
Psychiatric Disorders	Suicide attempt ^b	1 (1.7)
Reproductive System and Breast Disorders	Vulvovaginal discomfort	1 (1.7)

Source: Adapted from Table 12.2 of the Clinical Study report.

Note: ^aSingle subject (Subject ^{(b) (6)}) experienced more than one TEAE. ^bThis treatment emergent adverse event was also classified as a serious adverse event (SAE).

Medical Reviewer's Comment

A single subject (Subject ^{(b) (6)}) (1.7%; 1 of 6) reported a total of 4 TEAEs: 3 under the GI SOC which were coded to the preferred terms (PT) constipation, nausea and vomiting and 1 TEAE under the Musculoskeletal and Connective Disorders SOC, coded to the PT back pain. All 4 AEs were mild, self-resolving and occurred on Study Day 8. Two subjects (3.3%, 2 of 6), one of whom was Subject ^{(b) (6)} listed above, reported back pain. On Study Day 7, a single subject reported a TEAE coded to the PT vulvovaginal discomfort. The Applicant deemed this TEAE to be "probably related" to the study drug. As mentioned earlier a single subject experienced an SAE (PT: suicide attempt) considered unrelated to the study drug.

This reviewer agrees with the Applicant that only one of the reported TEAEs, vulvovaginal discomfort, appears to be potentially causally related to administration of metronidazole vaginal gel. This AE is consistent with the adult Phase 3 registrational trial. However, one cannot exclude confounding by the treatment indication, given the patient's history of BV. There were no moderate or severe intensity TEAEs.

In comparison, 19.0% (61/321) of all subjects in the metronidazole vaginal gel 1.3% arm of the Phase 3 adult registrational trial, MG-1601-01, experienced at least one AE, with 8.1% of all subjects experiencing an AE under the Infection/Infestations SOC, including 18 subjects reporting an AE under the PT term vulvovaginal candidiasis (VVC.) AEs occurring in ≥ 1% of all adult subjects were as follows (in descending order): headache (7 patients; 2.2%); nausea (5 subjects; 1.6%); vulvovaginal pruritus (5 subjects; 1.6%); diarrhea (4 subjects; 1.2%); and 3 subjects (1.0%) each with abdominal pain, dry mouth and vulvovaginal burning

NUVESSA Vaginal Tolerability Assessment

Table 6 provides a tabular summary of vaginal tolerability parameters (inflammation, irritation, and itching) as captured both pre- (Study Day 1) and post (Study Day 8) NUVESSA administration.

Table 6 Summary of Vaginal Tolerability Assessment by Visit (Safety Population)

Tolerability Parameter	Assessment	Site Visit	
		Screening/Baseline Visit (Day 1) (N=60) n (%)	Safety Visit (Day 8) (N=58) n (%)
Inflammation ^b	Absent	20 (33.3)	51 (87.9)
	Mild	32 (53.3)	7 (12.1)
	Moderate	8 (13.3)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Irritation ^a	Absent	16 (26.7)	48 (82.8)
	Mild	37 (61.7)	10 (17.2)
	Moderate	7 (11.7)	0 (0.0)
	Severe	0 (0.0)	0 (0.0)
Itching ^a	Absent	14 (23.3)	54 (93.1)
	Mild	39 (65.0)	4 (6.9)
	Moderate	7 (11.7)	0
	Severe	0 (0.0)	0 (0.0)

Source: Adapted from Table 12-3 of the Clinical Study Report.

Notes: N=number of subjects in the Safety population; n=number of subjects in the Safety population with a vaginal tolerability assessment at the indicated site visit. ^aItching and irritation are vaginal symptoms, self-assessed by the subject. ^bInflammation was a vaginal sign, assessed by the investigator.

Medical Reviewer's Comment

As noted in Table 6, no subjects reported severe tolerability parameters (inflammation, irritation, or itching) at baseline. Most patients reported mild symptoms for all evaluated parameters at baseline, as illustrated above. However, by Study Day 8 post treatment most subjects reported tolerability parameters as being “absent,” albeit a few subjects still reported continuation of symptoms, none of which were assessed as either moderate or severe in intensity. Nonetheless, given the limited study size and the absence of a comparator drug, no definitive conclusions can be ascertained based on the information presented above.

8.4.6. Laboratory Findings

Since the test article was administered as a single application, no laboratory values were collected during the course of this study. Vaginal fluid and microbiologic assessments were conducted at the Screening/Baseline visits (Day 1) for evaluation of eligibility criteria only.

Medical Reviewer's Comment

The drug is not systemically absorbed, therefore, outside of baseline microbiologic testing, routine labs were not collected. Among collected laboratory assessments, no abnormalities were observed.

8.4.7. Vital Signs (VS)

Vital signs (VS) (i.e., systolic blood pressure, diastolic blood pressure, heart rate, and temperature) were collected at Screening/Baseline visits (Day 1).

Medical Reviewer's Comment

Upon review of Table 14.5.4.1, which provided descriptive statistics (i.e. mean, median, minimum and maximum) of all collected VS values at baseline among all subjects comprising the safety population, this clinical reviewer observed no VS abnormalities. VS were not collected at subsequent visits.

8.4.8. Electrocardiograms (ECG)

ECGs were not collected during this study.

8.4.9. QT

Not applicable since ECGs were not collected during this study.

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8.4.10. Immunogenicity

Nuvessa is not a peptide. Therefore, its potential for immunogenicity was not anticipated and immunogenicity was not evaluated during this study.

8.5. Analysis of Submission Specific Safety Issues

Not applicable.

Medical Reviewer's Comment

Based on the previously conducted adult trials, no safety specific issues were evaluated or identified for additional review in this trial.

8.6. Safety Analyses by Demographic Subgroups

There were no apparent safety differences by age, race or ethnicity in this small open-label trial with a total of 9 TEAEs occurring in 6 subjects.

Medical Reviewer's Comment

Limited subject numbers made it difficult to draw any definitive conclusions on any safety signals by demographic subgroups in this all adolescent female study.

8.7. Specific Safety Studies

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported during the study period.

8.8.3. Pediatrics and Assessment of Effects on Growth

This study satisfies a previous post-marketing requirement, PMR 2123-001.

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8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Nuvessa (metronidazole vaginal gel 1.3%) is a single-dose, intravaginally administered pre-filled disposable applicator with limited systemic absorption and therefore has no drug abuse, drug withdrawal, or drug rebound potential.

8.9. Safety in the Postmarket Setting

There are no safety issues pertaining to Nuvessa that have been identified in the postmarket setting.

8.10. Integrated Assessment of Safety

In this relatively small open-label study evaluating Nuvessa's safety and tolerability in adolescent females, few subjects (6/60; 10%) experienced a treatment emergent adverse event (TEAE). Of the captured events, vulvovaginal discomfort is determined by this reviewer to be most likely related to Nuvessa. There were no deaths and no treatment discontinuations due to any reported AEs. Only a single SAE was reported, a suicide attempt, and this event was assessed by both this reviewer and the Applicant as being unrelated to the study drug. Most reported TEAEs were described as mild intensity events. A single TEAE, vulvovaginal discomfort, was deemed "probably related" to the study drug.

In summary, Nuvessa's overall safety profile in pediatric patients aged 12 to <18 years old is comparable to the safety observed in adult women ≥18 years old.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this submission.

10. Labeling Recommendations

Key clinical changes to the Applicant's proposed label are addressed in this section. Each number below corresponds to a section in the label.

Section 1 Indications and Usage

The review team updated this section to expand the treatment indication to include "females 12 years of age and older" diagnosed with BV.

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Section 6 Adverse Reactions

The review team updated this section to provide a brief description of the pediatric safety study, including a listing of all TEAEs occurring in $\geq 1\%$ of subjects.

Section 8.4 Pediatric Use

This section indicates that Nuvessa's safety and efficacy has not been established for pediatric patients younger than 12 years of age. This section further informs that established safety in adolescent females ages 12 to <18 years old was obtained from 60 patients enrolled in an open-label safety and tolerability study.

11. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies (REMS) were applicable to this submission.

12. Postmarketing Requirements and Commitments

With the 19 December 2017 sNDA submission of the clinical study report for Protocol 1401 entitled "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", the Applicant has fulfilled postmarketing requirement PMR 2123-001 and any other postmarketing commitments acknowledged in the original 24 March 2014 approval letter.

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13. Appendix

Clinical Investigator Financial Disclosure Review Template

Application Number:

NDA 205,223

Submission Date(s): February 5, 2018

Applicant: Chemo Research, SL

Product: Metronidazole Vaginal Gel 1.3% (NUVESSA)

Reviewer: Caroline J. Jjingo, MD, MPH

Date of Review: June 15, 2018

Covered Clinical Study (Name and/or Number): **MG-1401**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 130 investigators; 33 of whom were investigators in the 5 clinical sites that enrolled subjects		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____		
Significant payments of other sorts: _____		
Proprietary interest in the product tested held by investigator: _____		
Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	Not Applicable <input checked="" type="checkbox"/> (Request details from applicant)

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Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	Not Applicable <input checked="" type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	Not Applicable <input checked="" type="checkbox"/> (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CAROLINE J JJINGO
07/19/2018

THOMAS D SMITH
07/19/2018
I concur.

SUMATHI NAMBIAR
07/20/2018
I agree with Dr. Jjingo's assessment.