STATISTICAL REVIEW AND EVALUATION

NDA #:	NDA 205223 Efficacy Supplement- 2 (SDN 64) PMR Final Study Report (SDN 63)
Related IND #:	IND 107484
Product Name:	Nuvessa (metronidazole vaginal gel, 1.3%)
Indication(s):	Treatment of bacterial vaginosis
Applicant:	Chemo Research SL
Dates:	Stamp date: February 5, 2018 (SDN 64) December 19, 2017 (SDN 63) PDUFA date: August 5, 2018 Review date: May 23, 2018
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Cheryl Dixon, Ph.D.
Concurring Reviewers:	Karen Higgins, Sc.D.
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Caroline Jjingo MD, Clinical Reviewer Tom Smith MD, Clinical Team Leader
Project Manager:	Jane Dean, RN, MSN

1. Background

Nuvessa was approved for the treatment of bacterial vaginosis (BV) in nonpregnant women on March 24, 2014. Given the similarities of BV in adolescent females as compared to adult females, efficacy of Nuvessa in adolescent females can be based on extrapolation of the efficacy seen in adult females. However, safety of Nuvessa needed to be evaluated in the adolescent female population.

Post marketing requirement (PMR) 2123-001 required the conduct of a study to evaluate the safety of metronidazole vaginal gel 1.3% single dose in the treatment of bacterial vaginosis in females 12 to <18 years of age. Study MG1401 was conducted to satisfy PMR 2123-001. The study report for Study MG1401 was submitted to the NDA on December 19, 2017. In this submission, the Applicant requested a revision of the indication to include females 12 to <18 years. The Applicant was informed that since there would be an expansion of the indicated population, submission of an efficacy supplement would be required for administrative purposes. Thus, the Applicant submitted an efficacy supplement on February 5, 2018 referencing the December 19, 2017 submission.

Study MG1401 is 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". Since efficacy in the adolescent female population is based on extrapolation of the efficacy seen in adult females, the evaluation of efficacy was limited to an assessment of the presence of vaginal discharge and odor as reported by the subject in a daily diary up to the Day 8 (± 2 days) Safety Visit. Additionally, the study was uncontrolled. Therefore, this review will consist of a brief description of the study design and summary of the study results.

2. Study MG1401

Study MF1401 was a multicenter, uncontrolled study designed to evaluate the safety and tolerability of a single dose of metronidazole vaginal gel 1.3% for the treatment of BV in postmenarcheal, adolescent females 12 to 17 years of age. The study was conducted at 5 investigational centers in the United States. Subjects were evaluated at 2 time points: screening/baseline on Day 1 and at a Safety Visit on Day 8 (± 2 days).

Patient eligibility was determined at the screening/baseline visit. Postmenarcheal, adolescent females 12 to < 18 years of age with a clinical diagnosis of BV were enrolled. A clinical diagnosis of BV is defined as having an off-white, thin, homogenous discharge, presence of clue cells ≥20%, vaginal pH ≥4.7, and a positive 10% KOH whiff test. There was no requirement to have a Nugent score > 4. Subjects with a known or suspected other infectious cause of vulvovaginitis (e.g. candidiasis, *T. vaginalis)* were to be excluded. Eligible subjects were enrolled and dispensed a single dose of metronidazole vaginal gel 1.3% to be applied intravaginally at bedtime on Day 1. Subjects returned to the clinic on Day 8 (±2 days) for a Safety visit where adverse events and concomitant medications were reviewed, and a vaginal exam and evaluation of vaginal tolerability was performed. Subjects who administered the study drug recorded the presence of vaginal discharge and odor in a daily diary each night at bedtime until the night before the Safety Visit.

The primary objective of the study was to evaluate the safety and tolerability of metronidazole vaginal gel 1.3%. Safety evaluations were performed on all subjects who self-administered the test article, and included treatment-emergent adverse event (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation. Vaginal tolerability, in terms of presence and severity of itching, irritation (by subject's description), and inflammation (by investigator's observation) was also assessed. The secondary objective was to evaluate the efficacy of metronidazole vaginal gel 1.3%. Efficacy was assessed by the daily presence of vaginal discharge and odor as reported by the subject in the diary beginning on Day 1 prior to dosing and ending on the night before the Safety Visit. No other assessment of efficacy was conducted.

A total of 60 subjects were enrolled in the study. All subjects in the enrolled population self-administered study drug and comprise the Safety population. The Per-Protocol (PP) population included all subjects in the Safety population who completed the study and did not have any major protocol violations. Two subjects were lost to follow-up and did not complete the study. There were no major protocol violations. Therefore, the PP population included 58 subjects.

The mean age of the female subjects was 15.3 years with a range from 12 to 17 years. Subjects were primarily Black (29, 48.3%) or White (27, 45.0%). Four subjects (6.7%) were of other race.

A summary of vaginal discharge and odor symptoms at Day 1 and Day 6 for the PP population are presented in Table 1. Day 1 is the day the subject administered the treatment and the assessment was made prior to dosing. The diary was to be kept until the night before the safety visit which could occur on Day 8 ± 2 days. All subjects completed a diary entry on Day 6 and therefore Day 6 was considered the most complete for the efficacy assessment. On Day 1, most subjects reported both discharge and odor (69.0%). By Day 6, 65.5% of subjects reported no symptoms. Of the subjects who still reported symptoms at Day 6, most reported discharge only (27.6%). Two patients reported odor only and an additional 2 subjects reported both discharge and odor being present at Day 6.

Table 1
Vaginal Discharge and Odor Symptoms (PP Population)

Time Point	Symptoms	n (%) N=58
Day 1	No symptoms	3 (5.2)
	Discharge only	14 (24.1)
	Odor only	1 (1.7)
	Both discharge and odor	40 (69.0)
Day 6	No symptoms	38 (65.5)
	Discharge only	16 (27.6)
	Odor only	2 (3.4)
	Both discharge and odor	2 (3.4)

Source: Adapted from Table 11-1 and Listing 16.2.6.1 of study report.

Reviewer's Comment: *It should be noted the results for Day 1 are slightly different than those reported in Table 11-1 of the study report. Table 11-1 of the study report presents Day 1 symptoms for 57 rather than 58 subjects. This is because one subject administered the test article the day after screening/baseline visit. However, Day 1 as reported above is based on the day the study drug was administered.*

All subjects were adolescent (aged 12 to 17) females. Therefore, a summary of the results is not reported for age and gender subgroups. Table 2 summarizes the vaginal discharge and odor symptoms at Day 1 and Day 6 for the PP population by race. The results by race indicate that the majority of Black and White subjects reported no symptoms at Day 6. However, slightly fewer Black subjects (62.1%) than White subjects (72.0%) reported no symptoms at Day 6. This finding is consistent with findings in the adult population with BV where Black subjects typically have lower response rates than White subjects.

Table 2
Vaginal Discharge and Odor Symptoms by Race (PP Population)

Time Point	Race	Symptoms	n (%)
Day 1	White (N=25)	No symptoms	1 (4.0)
		Discharge only	5 (20.0)
		Odor only	1 (4.0)
		Both discharge and odor	18 (72.0)
	Black (N=29)	No symptoms	2 (6.9)
		Discharge only	6 (20.7)
		Odor only	0
		Both discharge and odor	21 (72.4)
	Other (N=4)	No symptoms	0
		Discharge only	3 (75.0)
		Odor only	0
		Both discharge and odor	1 (25.0)
Day 6	White (N=25)	No symptoms	18 (72.0)
		Discharge only	5 (20.0)
		Odor only	2 (8.0)
		Both discharge and odor	0
	Black (N=29)	No symptoms	18 (62.1)
		Discharge only	9 (31.0)
		Odor only	0
		Both discharge and odor	2 (6.9)
	Other (N=4)	No symptoms	2 (50.0)
		Discharge only	2 (50.0)
		Odor only	0
		Both discharge and odor	0

Source: Adapted from Listing 16.2.6.1 of study report.

Six subjects (10.0%) in the Safety population experienced at least 1 treatment emergent adverse event. There were no deaths or discontinuations due to adverse events during the study. The safety profile was consistent with the known safety profile for the adult population and no new safety concerns were identified. See the Clinical Reviewer's review for a detailed review of the safety data.

3. Conclusions

Efficacy of metronidazole vaginal gel 1.3% for the treatment of BV has been established in the adult female population. Given the similarities of BV in the adolescent population, efficacy is primarily extrapolated from the adult female population. The limited efficacy provided from the Phase IV study in adolescent females does not indicate that extrapolation is not reasonable. The results of the Phase IV study showed what can be considered a clinically relevant response of 65.5% of subjects being symptom free (based on vaginal discharge and odor) by Day 6 and are consistent with the known efficacy profile in the adult population.

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/s/

CHERYL A DIXON
05/23/2018

KAREN M HIGGINS
05/24/2018
I concur.