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Original Research

Single-Dose, Bioadhesive Clindamycin 2% Gel for Bacterial Vaginosis

A Randomized Controlled Trial

Christine Mauck, MD, MPH, Sharon L. Hillier, PhD, Judy Gendreau, MD, Clint Dart, MS, Steven Chavoustie, MD, Valerie Sorkin-Wells, MD, Clifton Nicholson-Uhl, MD, Brandon Perez, MD, Mark Jacobs, MD, Nadene Zack, MS, and David Friend, PhD

OBJECTIVE: To assess efficacy and safety of a single-dose vaginal clindamycin gel for bacterial vaginosis treatment.

METHODS: We conducted a double-blind, placebo-controlled, randomized study comparing clindamycin gel with placebo (2:1 ratio). Entry required clinical diagnosis of bacterial vaginosis, that is, all four Amsel's criteria, without other genital infections. Nugent scores of 7–10 were required for efficacy assessment, per updated 2019 U.S. Food and Drug Administration guidance. Patients were evaluated at screening, day 7–14, and day 21–30 (test of cure). *Clinical cure* was defined as resolution of three of four Amsel's criteria. *Bacteriologic cure* was defined as Nugent score lower than 4. Therapeutic cure was both clinical and bacteriologic cure. Primary outcome was clinical cure at the test-of-cure visit. Secondary endpoints were clinical cure at day 7–14, and bacteriologic and therapeutic cures at day 7–14 and test of cure. A sample size of 188 patients in the clindamycin group compared with 94 patients in the placebo group had 90% power to detect statistically significant difference (P=.05, 2-tailed).

RESULTS: Participants were seen between July 9, 2020, and November 12, 2020. Of 307 randomized women, 56.0% were Black and 88.3% reported one or more previous bacterial vaginosis episodes. In the modified intention-to-treat population, 70.5% of patients in the clindamycin group and 35.6% in the placebo group achieved clinical cure at test of cure (primary outcome) (difference of 34.9, 95% CI 19.0–50.8), as did 77.5% of patients in the clindamycin group and 42.6% of patients in the placebo group in the per-protocol population (dif-

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Corresponding author: Christine Mauck, MD, MPH, Daré Bioscience, Inc., San Diego, CA; email: cmauck@darebioscience.com.

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Christine Mauck, David Friend, and Nadene Zack are or were paid employees of Daré Bioscience, Inc. and hold stock options or stock. Sharon L. Hillier is employed by Magee-Womens Research Institute, Pittsburgh, PA, which provided consulting services to Daré Bioscience, Inc. She also received consulting fees from Daré Bioscience, Inc. Judy Gendreau is a partner of Gendreau Consulting, LLC, a consultant to Daré Bioscience, Inc. and has received cash consulting fees and shares of Daré Bioscience, Inc. common stock. Her husband, R. Michael Gendreau, is also a consultant for Daré Bioscience, and as such, he also has received consulting fees, paid to Gendreau Consulting, LLC. He also was provided with stock as payment for consulting services provided to Daré prior to the company's initial financing. Clint Dart is employed by Health Decisions, Inc., a company engaged by Daré Bioscience, Inc. to assist in the conduct of the study. Steven Chavoustie, Valerie Sorkin-Wells, Clifton Nicholson-Uhl, Brandon Perez, and Mark Jacobs were study investigators and are employed by institutions that received cash compensation from Daré Bioscience, Inc. for their participation.

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ference of 34.9, 95% CI 17.0–52.7). Statistically significant differences between groups were seen for all secondary endpoints. Clinical cure rate in patients in the clindamycin group with more than three bacterial vaginosis episodes in the prior year was 70.0%. Approximately 15% (15.3%) of patients in the clindamycin group experienced one or more treatment-emergent adverse events related to study treatment, as did 9.7% of patients in the placebo group. The most frequent treatment-related, treatment-emergent adverse event was vulvovaginal candidiasis.

CONCLUSION: A new, single-dose clindamycin vaginal gel was highly effective, with excellent safety, in women disproportionately affected by bacterial vaginosis, with Nugent scores of 7–10 at study entry.

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Bacterial vaginosis is the most common vaginal infection in women of childbearing age. It is associated with disruption in normal vaginal microbiota, with a decrease in lactic acid–producing bacteria and an increase in various anaerobes, including *Gardnerella vaginalis*, *Atopobium vaginae*, and others.[1] The cause of bacterial vaginosis is not fully understood; treating male sex partners does not prevent recurrence.[2] The prevalence of bacterial vaginosis varies by race and ethnicity; it has been reported in 51% of non-Hispanic Black women and 32% of Mexican-American women compared with 23% of non-Hispanic White women.[3]

Symptoms of bacterial vaginosis include a thin white or gray vaginal discharge; pain, itching, or burning in the vagina; a strong fish-like odor, especially after sex; burning when urinating; and itching around the outside of the vagina.[4] Bacterial vaginosis is associated with increased risk of pelvic inflammatory disease, infertility, adverse pregnancy outcomes, and sexually transmitted infections including HIV.[1]

The reference standard laboratory method for diagnosing bacterial vaginosis is the Nugent score, using a Gram stain to determine the concentration of long gram-positive rods (lactobacilli), and the small gram-negative and gram-variable rods and curved gram-negative rods associated with bacterial vaginosis. A Nugent score of 0–3 is considered normal, 4–6 intermediate, and 7–10 diagnostic of bacterial vaginosis.[5]

The Nugent score requires a moderate-complexity laboratory and is therefore not available as a point-of-care test. Clinical diagnosis is based on Amsel's criteria, which requires the presence of three of the following four signs: homogeneous, thin discharge (milk-like consistency) that smoothly coats the vaginal walls; clue cells (vaginal epithelial cells studded with adherent bacteria) on microscopic examination; pH of vaginal fluid greater than 4.5; and a fishy odor of vaginal discharge after addition of 10% potassium hydroxide (ie, the "whiff test").[4,6] The sensitivity and specificity of the Amsel criteria are 37–70% and 94–99%, respectively, compared with Nugent scoring.[7]

XACIATO ("zah-she-AH-toe," clindamycin phosphate) was approved by the U.S. Food and Drug Administration (FDA) in 2021 for the treatment of bacterial vaginosis. It is unique among bacterial vaginosis treatments in that it is a thermosetting bioadhesive intravaginal gel formulated with 2% clindamycin phosphate designed to release the active ingredient for an extended period of time.[8] At room temperature, the product is a viscous liquid that transitions to a temporary self-forming polymeric gel at body temperature with no alteration in the product's chemical composition. This phase change results in increased viscosity, rendering it immobile, which is designed to reduce leakage and improve vaginal retention time. Reduced leakage should result in better user compliance, and, because clindamycin is more effective with increased exposure time, the increased retention time should result in higher cure rates.[9–14] The safety and efficacy of vaginal clindamycin phosphate has been widely demonstrated in prior work.[15]

The primary objective of this study was to assess efficacy of the new vaginal clindamycin gel for bacterial vaginosis treatment, based on the proportion of patients demonstrating clinical cure at day 21–30 postadministration. Secondary objectives were to assess safety and acceptability. Efficacy and safety are described here; user acceptability will be described separately.

METHODS

This was a double-blind, placebo-controlled, randomized study comparing the efficacy, safety, and acceptability of a 2% clindamycin vaginal gel for bacterial vaginosis treatment, compared with the hydroxyethylcellulose universal placebo gel, which has served as the control in several vaginal product clinical trials accepted by the FDA.[16] The study design was consistent with the August 2019 FDA guidance titled, "Bacterial Vaginosis: Developing Drugs for Treatment."[17] The study followed principles set forth in the Helsinki Declaration of 1975, as revised in 2013. It was

reviewed per federal regulations and ICH guidelines by the Advarra Institutional Review Board.

Eligibility criteria are shown in Appendix 1, available online at http://links.lww.com/AOG/C723. Volunteers had a clinical diagnosis of *bacterial vaginosis*, defined as meeting all four Amsel's criteria. At screening, specimens were also collected for Nugent scoring, OSOM™ testing for trichomoniasis, nucleic acid amplification testing for chlamydia and gonorrhea, and potassium hydroxide wet mount and vaginal culture for yeast. Participants could not have active vulvovaginitis or other active infectious causes of cervicitis, vaginitis, or vulvitis, based on these assessments and clinical examination, and could not have genital lesions or ulcers consistent with human papillomavirus, herpes simplex virus, syphilis, or chancroid.

If there was any ambiguity in the patient's signs, symptoms, or microscopic assessments suggesting a mixed infection, randomization and treatment were delayed until yeast culture and nucleic acid amplification test results were available, assuming the patient was able and willing to delay treatment for several days. If either test result was positive, or if it was not feasible to delay treatment, the patient was screen-failed.

If, however, screening assessments supported the diagnosis of bacterial vaginosis only and the patient was randomized, but it was later learned that the *Candida* culture was positive at screening, the investigator assessed whether antifungal therapy was clinically warranted, or if the culture represented a subclinical condition not requiring treatment. An adverse event was recorded only if the patient required treatment for signs or symptoms consistent with a yeast infection; that is, a positive culture by itself did not constitute an adverse event.

This study differed from efficacy studies of other bacterial vaginosis treatments in two important respects, aimed at strengthening the diagnosis of bacterial vaginosis at screening. This study followed the 2019 FDA guidance for studies of bacterial vaginosis treatments that required women in the modified intention-to-treat (ITT) population to have Nugent scores of 7–10 at screening. Efficacy studies of other approved bacterial vaginosis treatments included women with intermediate Nugent scores of 4–6. In addition, vaginal *Candida* cultures were obtained at screening; women with positive cultures were excluded from the modified ITT population.

Patients were evaluated at three timepoints: day 1 (screening and randomization), day 7–14 (interim assessment), and day 21–30 (test of cure). *Clinical cure* was defined as resolution of three of four Amsel's criteria, namely: absence of the abnormal vaginal discharge consistent with bacterial vaginosis as determined by the investigator, negative whiff test, and the presence of less than 20% clue cells. The fourth Amsel criterion, vaginal pH, was not part of the primary endpoint, per the 2019 FDA guidance.[17] *Bacteriologic cure* was defined as a Nugent score lower than 4, and therapeutic cure as both a clinical cure and bacteriologic cure.

The primary efficacy endpoint was clinical cure at the test-of-cure visit (day 21–30). The secondary efficacy endpoints were clinical cure at the interim visit, and bacteriologic cure and therapeutic cures at the interim and test-of-cure visits.

The following five populations were defined. The all-screened population was all patients who signed the consent form and were screened. The ITT population was all randomized patients. The safety population was all patients in the ITT population who applied study drug. The modified ITT population consisted of the safety population patients, except those excluded owing to a positive baseline test result for other vaginal or cervical infections (eg, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Candida* species) or a baseline Nugent score lower than 7. The per-protocol population was comprised of patients in the modified ITT group who met the following criteria: met all four Amsel's criteria at screening, applied assigned study drug within 1 day of randomization, did not use a prohibited medication before the day 21–30 visit, attended the day 21–30 visit, and had no other major protocol violations that affected the primary or secondary endpoints.

In the event of persistent bacterial vaginosis symptoms, patients could be offered other bacterial vaginosis treatment before study completion. For the modified ITT and per-protocol populations, if the patient received other therapy for bacterial vaginosis, she was included in the analysis as a treatment failure for all visits on or after receipt of bacterial vaginosis therapy. Patients who received bacterial vaginosis therapy for a diagnosis other than bacterial vaginosis (eg, trichomoniasis) were excluded from the per-protocol population.

Clindamycin and placebo gel were supplied in matching 25g tubes with applicators and instructions. One applicator dispensed 5 g of study product (100 mg clindamycin, the same dose delivered by marketed vaginal clindamycin bacterial vaginosis treatments [Cleocin, Clindesse]). Patients were randomized in a blinded manner to clindamycin or placebo in a 2:1 ratio, stratified by study site and race.

The study site staff were blinded to study treatment throughout the study.

At screening and randomization (day 1), bacterial vaginosis history, signs, and symptoms were evaluated. A saline wet mount to assess clue cell percentage and other findings (eg, trichomonads), 10% potassium hydroxide whiff test and wet mount microscopy for yeast assessment, vaginal *Candida* culture, vaginal pH, preparation of slides for centralized Nugent scoring, urine pregnancy test, nucleic acid amplification tests for *C trachomatis* and *N gonorrhoeae*, OSOM test for *Trichomonas vaginalis*, blood sample for chemistry and hematology, and urinalysis were done.

A major goal of screening was to confirm the presence of bacterial vaginosis and to rule out other causes of vulvovaginitis. Careful attention was therefore paid to both the clinical and microscopic assessments. However, the literature suggests that these assessments are less than optimal at identifying patients with candidiasis[18,19]; therefore, a vaginal *Candida* culture was obtained to determine whether the patient was to be included in the modified ITT population.

After screening, eligible patients were randomized in a blinded manner using validated, access-controlled interactive response technology to a single dose of clindamycin gel or placebo gel. Study drug was applied intravaginally within 1 day of randomization. Stratification factors in the randomization included study site and race (Black or African American vs all others). A randomization number was automatically provided by the interactive response technology system and confirmed by email, ensuring concealment of treatment allocation.

At visit 1, patients were given an electronic diary (eDiary) to collect information regarding administration of study drug (single dose, administered at home, ideally in the evening after visit 1), bacterial vaginosis symptoms, adverse events, and other information. Study staff reviewed eDiaries at each visit.

Patients returned to the site on day 7–14 for the interim visit, and on day 21–30 for test of cure. The investigator performed gynecologic examinations and collected specimens for the following tests: saline wet mount for clue cells, 10% potassium hydroxide whiff test and wet mount yeast assessment, vaginal pH, centrally scored Nugent score, urinalysis, and urine pregnancy test. Signs and symptoms of bacterial vaginosis including color, odor, and consistency of vaginal discharge, plus vulvovaginal itching and irritation were evaluated at each visit. Posttreatment chemistry and hematology assessments were obtained at the test-of-cure visit. If clinical symptoms (supported by microscopic findings) indicated active vulvovaginal candidiasis at the interim or test-of-cure visit, a vaginal yeast culture was obtained. Adverse events were assessed at each visit, as were patient-reported and investigator-assessed local site reactions. Patients were to abstain from sexual activity throughout the first 7 days after treatment, and from using intravaginal products through the first 7 days at least, and ideally through test of cure.

Primary efficacy analyses were conducted on the modified ITT population. Hypothesis testing for the secondary efficacy endpoints in the modified ITT population was conducted in a sequential manner to control the overall type 1 error rate. If any of the endpoints had not met the $P \leq .050$ level, all hypothesis testing would have stopped. Supportive efficacy analyses were performed in the per-protocol population. Safety analyses were performed on the safety population. Patients were analyzed according to the treatment to which they were randomized for ITT and modified ITT analyses. For other analysis populations, patients were analyzed by treatment received.

SAS 9.4 was used for analysis. A sample size of 188 clindamycin patients compared with 94 patients in the placebo group had 90% power to detect a statistically significant difference at a significance level of 0.05 (2-tailed) under the assumption that the clinical cure rates were 55% and 30% for clindamycin and placebo, respectively. This sample size assumed 35% of randomized patients were not in the modified ITT population. If the *P*-value from the Cochran-Mantel-Haenszel χ^2 test (which was stratified by site and race, the latter categorized as Black and all other races) was $\leq .05$, the null hypothesis that the clinical cure rates in the clindamycin and placebo groups were equal was rejected.

RESULTS

The study was initiated at 36 U.S. sites and enrolled at 32. The first participant was consented on July 9, 2020, and the last contact was on November 12, 2020. A total of 307 patients were randomized (Table 1 and Fig. 1); 17 (5.5%) patients prematurely discontinued, and 290 (94.5%) patients completed the study. Most patients who failed to complete were lost to follow-up, although the lost-to-follow-up rate was low (2.9%). Appendix 2, available online at http://links.lww.com/AOG/C723, shows each study population.

Mean (SD) age at study entry was 34.8 years (8.84) (Table 2). The majority of patients were Black (56.0%) and not Hispanic or Latina (74.5%). Age, race, weight, height, and body mass index (BMI, calculated as weight in kilograms divided by height in meters

Table 1. Patient Disposition and Reasons for Discontinuation, All-Screened Population*

		Treatment Group		
	Screen Failure (n=206)	Clindamycin (n=204)	Placebo (n=103)	Total (N=513)
Total consented	206 (100)	204 (100)	103 (100)	513 (100)
Total screen fails	206 (100)			206 (40.2)
Total randomized		204 (100)	103 (100)	307 (59.8)
Completed the study		190 (93.1)	100 (97.1)	290 (94.5)
Early discontinued		14 (6.9)	3 (2.9)	17 (5.5)
Reason for early discontinuation				
Retrospective discovery of entry criterion violation		0	0	0
Treatment failure		0	0	0
Occurrence of other vaginal infection requiring treatment		0	0	0
Other adverse event		0	0	0
Withdrawal of consent		6 (2.9)	1 (1.0)	7 (2.3)
Lack of compliance		0	0	0
Lost to follow-up		7 (3.4)	2 (1.9)	9 (2.9)
Other		1 (0.5)	0	1 (0.3)

Data are n (%).
* Percentages for study completion, early discontinuation, and reasons for early discontinuation are based on the number of participants randomized within each treatment group.

squared) were evenly distributed between the treatment groups. A somewhat larger proportion of patients in the modified ITT group were Black compared with the ITT population (64.1% vs 56.0%, respectively, data not shown). Most patients (88.3%) reported at least one previously diagnosed bacterial vaginosis episode in their lifetime, and 75.9% reported at least one episode in the past 12 months. The treatment most commonly used in the previous 12 months was oral or intravaginal metronidazole.

In the modified ITT group population, the proportion of patients achieving clinical cure at test of cure (day 21–30) was statistically significantly higher in the clindamycin group (70.5%) than placebo (35.6%) (difference of 34.9, 95% CI 19.0–50.8, $P<.001$, Table 3). Results in the ITT population were similar (Appendix 3, available online at http://links.lww.com/AOG/C723). In the per-protocol population, clinical cure rates at test of cure were higher in both groups than in the modified ITT population, and the rate in the clindamycin group was again significantly higher than the placebo group (77.5% vs 42.6%, respectively, difference of 34.9, 95% CI 17.0–52.7, $P<.001$). The P-value was $\leq.001$ for each of the secondary endpoint analyses in the modified ITT group (Table 3). The clinical cure rate among patients in the clindamycin group with more than three bacterial vaginosis episodes in the past 12 months was 70.0% (Table 4).

Overall, 104 (34.0%) patients experienced one or more *treatment-emergent adverse events*, defined as any adverse event that developed or worsened in severity or frequency after study drug administration (Table 5 and Appendix 4, available online at http://links.lww.com/AOG/C723). No treatment-emergent adverse events led to early discontinuation. Most patients who experienced a treatment-emergent adverse event experienced a mild one. One patient in the placebo group experienced two severe treatment-emergent adverse events (trichomoniasis and pelvic infection) and was diagnosed with cervical carcinoma, a serious adverse event. There were two severe treatment-emergent adverse events in the clindamycin group (severe somnolence and severe vulvovaginal pruritus) but no serious adverse events.

Overall, 15.3% of patients in the clindamycin group experienced one or more treatment-emergent adverse events that were possibly, probably, or definitely related to study treatment, as did 9.7% of patients in the placebo group (data not shown). The most frequently reported treatment-related treatment-emergent adverse events were vulvovaginal candidiasis (9.4% of patients in the clindamycin group vs 1.0% of patients in the placebo group) and vulvovaginal pruritus (2.0% of patients in the clindamycin group vs 1.0% of patients in the placebo group) (Table 6). In both groups, at least half of the candidiasis occurred in patients with

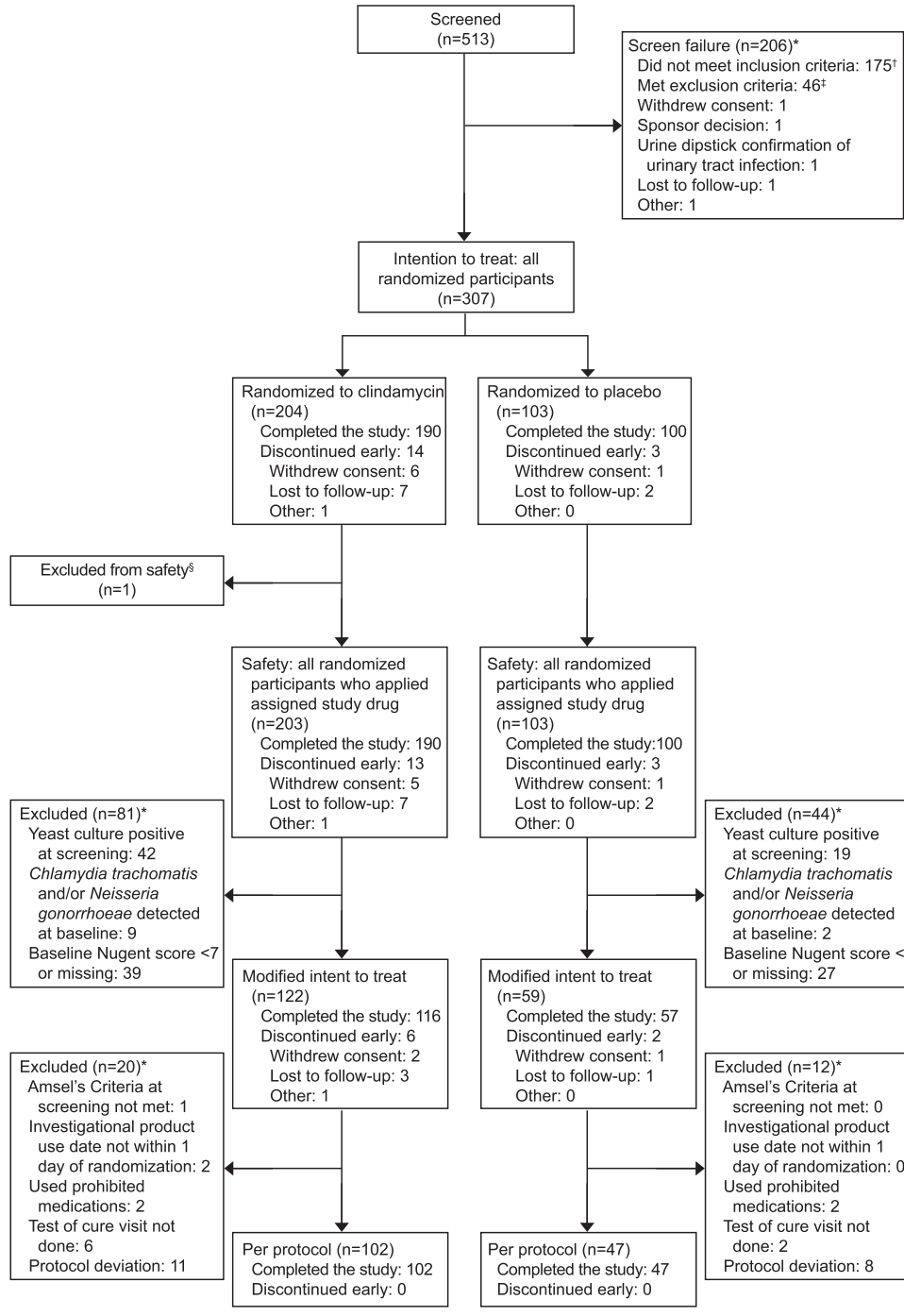

Fig. 1. Disposition of patients. *Items not mutually exclusive. †Clinical diagnosis of bacterial vaginosis (n=174); females aged 12 years or older with no known medical conditions that, in the investigator's opinion, may interfere with study participation (n=1). ‡Active vulvovaginitis or other infectious causes of cervicitis, vaginitis, or vulvitis per clinical assessments and in-clinic microscopic assessments (n=32); vaginal, vulvar, or genitourinary condition that, according to the investigator's judgment, may confound the interpretation of clinical response (n=7); currently receiving or who have received antifungal or antibacterial therapy (systemic or intravaginal) within 14 days of the screening and randomization visit (n=1); will undergo evaluation or treatment during the study for abnormal cytology and/or findings from high-risk human papillomavirus testing and/or Pap test finding (n=1); history of any severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk in trial participation (n=5). §Participant returned investigational product.

Mauck. Single-Dose Clindamycin 2% Gel for Bacterial Vaginosis. Obstet Gynecol 2022.

positive yeast cultures before dosing: 51.4% (18/35) of patients in the clindamycin group and 50.0% (2/4) of patients in the placebo group (Appendix 5, available online at http://links.lww.com/AOG/C723).

Three types of patient-reported local site reactions were recorded: pruritus, burning or stinging, and vulvovaginal pain. Pruritus was most common, reported by 37.4% of patients in the clindamycin group and 38.8% of patients in the placebo group before treatment. At the interim visit, pruritus had decreased to 21.8% of patients in the clindamycin group and 15.7% of patients in the placebo group. At the test-of-cure visit,

Table 2. Demographics, Intention-To-Treat Population

Demographic	Treatment Group		
	Clindamycin (n=204)	Placebo (n=103)	Total (N=307)
Age (y)			
n	204	103	307
Mean±SD	34.6±8.8	35.2±9.0	34.8±8.8
Median	34	35	35
25th, 75th percentile	27.0, 40.0	27.0, 41.0	27.0, 40.0
Minimum, maximum	15, 56	19, 59	15, 59
Age (y)			
n	204	103	307
20 or younger	5 (2.5)	1 (1.0)	6 (2.0)
21–30	66 (32.4)	33 (32.0)	99 (32.2)
31–40	84 (41.2)	42 (40.8)	126 (41.0)
41–50	41 (20.1)	20 (19.4)	61 (19.9)
51 or older	8 (3.9)	7 (6.8)	15 (4.9)
Ethnicity			
n	203	103	306
Hispanic or Latina origin	57 (28.1)	21 (20.4)	78 (25.5)
Not Hispanic or Latina origin	146 (71.9)	82 (79.6)	228 (74.5)
Race			
n	204	103	307
American Indian or Alaska Native	2 (1.0)	0	2 (0.7)
Asian	1 (0.5)	1 (1.0)	2 (0.7)
Black or African American	116 (56.9)	56 (54.4)	172 (56.0)
Native Hawaiian or other Pacific Islander	2 (1.0)	1 (1.0)	3 (1.0)
White	82 (40.2)	44 (42.7)	126 (41.0)
Not reported	1 (0.5)	1 (1.0)	2 (0.7)
Unknown	0	0	0
Weight at study entry (kg)			
n	204	103	307
Mean±SD	84.6±25.45	82.3±24.6	83.8±25.1
Median	80.2	78.0	78.9
25th, 75th percentile	64.9, 98.2	66.2, 91.6	65.5, 96.2
Minimum, maximum	45.8, 181.4	44.0, 190.1	44.0, 190.1
Height at study entry (cm)			
n	204	103	307
Mean±SD	162.9±6.4	163.2±7.7	163.0±6.9
Median	162.6	162.6	162.6
25th, 75th percentile	158.3, 167.6	157.5, 167.6	157.5, 167.6
Minimum, maximum	147.3, 182.9	132.1, 180.3	132.1, 182.9
BMI at study entry (kg/m^2)			
n	204	103	307
Mean±SD	31.8±8.7	30.8±8.2	31.5±8.5
Median	31.0	29.9	30.2
25th, 75th percentile	25.1, 37.1	25.1, 34.9	25.1, 36.3
Minimum, maximum	17.2, 60.9	17.8, 61.9	17.2, 61.9
BMI category at study entry (kg/m^2)			
n	204	103	307
Underweight (lower than 18.5)	2 (1.0)	1 (1.0)	3 (1.0)
Normal weight (18.5–24.9)	48 (23.5)	22 (21.4)	70 (22.8)
Overweight (25.0–29.9)	46 (22.5)	29 (28.2)	75 (24.4)
Obese (30.0 or higher)	108 (52.9)	51 (49.5)	159 (51.8)

BMI, body mass index.
Data are n (%) unless otherwise specified.

Table 3. Summary of Clinical Cure, Bacteriologic Cure, and Therapeutic Cure, Modified Intention-To-Treat Population*

	Treatment Group		
	Clindamycin (n=122)	Placebo (n=59)	Treatment Difference [% (95% CI)]
Parameter at the test-of-cure visit (day 21–30)			
Clinical cure (primary endpoint) (95% CI for the percentage)	86 (70.5) (62.0–79.0)	21 (35.6) (22.5–48.7)	34.9 (19.0–50.8)
Bacteriologic cure†	53 (43.4)	3 (5.1)	38.4 (26.7–50.1)
Therapeutic cure	45 (36.9)	3 (5.1)	31.8 (20.3–43.3)
Parameter at the interim assessment visit (day 7–14)			
Clinical cure	93 (76.2)	14 (23.7)	52.5 (38.0–67.0)
Bacteriologic cure†	50 (41.0)	2 (3.4)	37.6 (26.5–48.7)
Therapeutic cure	43 (35.2)	0	35.2 (25.5–45.0)

* *P*-values from Cochran-Mantel-Haenszel test with strata of study site and race (African American or all other races) <.001 for all rows.
† Nugent score lower than 4.

it was reported by 16.3% of patients in the clindamycin group and 12.0% of patients in the placebo group.

Burning or stinging was reported by 21.7% of patients in the clindamycin group and 23.3% of patients in the placebo group at baseline, decreasing to 9.8% of patients in the clindamycin group and 14.7% of patients in the placebo group at the interim visit. At the test-of-cure visit, it was reported by 6.3% of patients in the clindamycin group and 10.0% of patients in the placebo group. Vulvovaginal pain was reported by 10.8% of patients in the clindamycin group and 10.7% of patients in the placebo group at baseline, decreasing to 3.6% of patients in the clindamycin group and 3.9% of patients in the placebo group at the interim visit. At the test-of-cure visit, it was reported by 2.6% of patients in the clindamycin group and 1.0% of patients in the placebo group.

Of the four types of investigator-assessed local site reactions (erythema, edema, petechiae, and erosions), erythema was most common, seen in 20.9% of patients in the clindamycin group and 19.2% of patients in the placebo group at baseline, and decreasing to 10.9% of patients in both groups by the interim visit. At the test-of-cure visit, it was still present in 5.8% of patients in the clindamycin group and 9.1% of patients in the placebo group. Edema was observed in 11.2% of patients in the clindamycin group and 7.1% of patients in the placebo group at baseline, decreasing to 2.6% of patients in the clindamycin group and 2.0% of patients in the placebo group at the interim visit. At the test-of-cure visit, it was still present in 3.7% of patients in the clindamycin group and 2.0% of patients in the placebo group. Petechiae and erosions were rare. There were no findings of concern among hematologic results, serum chemistries, or urinalyses

Table 4. Primary Analysis of Clinical Cure for Patients in the Modified Intention-To-Treat Population by Bacterial Vaginosis History

	Treatment Group		Difference (Clindamycin−Placebo)
	Clindamycin	Placebo	
At most 3 episodes of BV diagnosed in past 12 mo	n=101	n=46	
n (%)	72 (71.3)	18 (39.1)	54 (32.2)*
95% CI for the percentage	62.0–80.6	23.9–54.3	13.9–50.4
More than 3 episodes of BV diagnosed in past 12 mo	n=20	n=13	
n (%)	14 (70.0)	3 (23.1)	11 (46.9)†
95% CI for the percentage	47.4–92.6	0.0–49.8	10.1–83.7

BV, bacterial vaginosis.
* *P*-values from Cochran-Mantel-Haenszel test with strata of study site and race (African American or all other races)=.001.
† As above, *P*=.010.

Table 5. Overall Number and Percentage of Patients With Adverse Events, Safety Population

	Treatment Group		
	Clindamycin (n=203)	Placebo (n=103)	Total (n=306)
Participants with at least 1 AE*	76 (37.4)	28 (27.2)	104 (34.0)
Severity†			
Mild	48 (23.6)	15 (14.6)	63 (20.6)
Moderate	26 (12.8)	12 (11.7)	38 (12.4)
Severe	2 (1.0)	1 (1.0)	3 (1.0)
Relatedness‡			
Unrelated	45 (22.2)	18 (17.5)	63 (20.6)
Possibly related	23 (11.3)	8 (7.8)	31 (10.1)
Probably related	5 (2.5)	2 (1.9)	7 (2.3)
Definitely related	3 (1.5)	0	3 (1.0)
Possibly, probably, or definitely related	31 (15.3)	10 (9.7)	41 (13.4)
Participants with at least 1 SAE	0	1 (1.0)	1 (0.3)
Death	0	0	0
Participants with at least 1 AE that led to early discontinuation§	0	0	0

AE, adverse event; SAE, serious adverse event.
Data are n (%).
* Adverse event coding dictionary: MedDRA 23.0.
† Participants reporting more than one AE are counted only once, in the category of greatest severity.
‡ Participants reporting more than one AE are counted only once, for the strongest relationship.
§ Based on a "yes" response to the AE Case Record Form question, "Did the adverse event cause the patient to be discontinued from the study?"

and no clinically relevant changes in vital sign or physical examination results.

DISCUSSION

A single intravaginal dose of a new clindamycin gel was significantly more effective than placebo in achieving a clinical cure at the test-of-cure (day 21–30) visit in the modified ITT population, the study's primary endpoint. Cure rates were even higher in the per-protocol population. The secondary endpoints of clinical cure at the interim visit, and bacteriologic and therapeutic cure at interim and test-of-cure visits also showed significant differences between clindamycin and placebo. The approximately 70% clinical cure rate was maintained

Table 6. Most Common Product-Related Treatment-Emergent Adverse Events (Observed in at Least 1% of Participants in Either Treatment Group), Safety Population

	Treatment Group					
	Clindamycin (n=203)			Placebo (n=103)		
Treatment-Emergent AE	Possibly Related	Probably Related	Definitely Related	Possibly Related	Probably Related	Definitely Related
Vulvovaginal candidiasis	12 (5.9)	4 (2.0)	3 (1.5)	1 (1.0)	0	0
Vaginal pruritus	4 (2.0)	0	0	0	1 (1.0)	0
Vaginal hemorrhage*	2 (1.0)	1 (0.5)	0	3 (2.9)	0	0
Bacterial vaginosis	1 (0.5)	0	0	1 (1.0)	0	0
Vaginal burning sensation	1 (0.5)	0	0	1 (1.0)	0	0
Vaginal discomfort	1 (0.5)	0	0	1 (1.0)	0	0
Urinary tract infection	1 (0.5)	0	0	1 (1.0)	0	0
Headache	0	0	0	1 (1.0)	0	0
Drug eruption	0	0	0	0	1 (1.0)	0

AE, adverse event.
Data are n (%).
* Includes the verbatim terms vaginal bleeding, vaginal petechiae, spotting not related to regular menstrual period, and dysfunctional bleeding.

even in women with multiple prior cases of bacterial vaginosis.

A limitation to this study was the need to follow the 2019 FDA guidance for bacterial vaginosis studies to determine which patients to include in the modified ITT analysis. Efficacy studies of other approved bacterial vaginosis treatments included women with intermediate Nugent scores of 4–6; this study used the more rigorous Nugent score criterion of 7–10. This may have biased the cure rates in this study downward, although even with this constraint, the cure rates seen were higher than those in other studies. Clinical cure rates cited in package inserts are 41.0% and 53.4% for Clindesse, 37.0% for Nuvessa, and 53.3% and 67.7% for Solosec (package inserts: Clindesse, Nuvessa, Solosec).

A study strength was obtaining vaginal *Candida* cultures from each patient; women with positive cultures were excluded from the modified ITT population. The study also enrolled a racially diverse population, with about two thirds of patients in the modified ITT population identifying as Black or African American. More than three quarters of patients reported having experienced bacterial vaginosis in the past 12 months, somewhat higher than published rates of up to 60% within 12 months of treatment. The study had a low lost-to-follow-up rate and almost all patients completed the study.

The product's safety profile was excellent, with most patients having no treatment-emergent adverse events, and the most common product-related treatment-emergent adverse event being, as expected, vulvovaginal candidiasis. The relationship between antibiotics such as clindamycin and development of candidiasis is well-known. It appears that having a positive yeast culture before receiving antibiotic treatment for bacterial vaginosis may predispose to candidiasis post–bacterial vaginosis treatment. Erythema, pruritus, burning, and stinging decreased over time in both groups but were still present in a higher percentage of patients in the placebo group at test of cure.

Bacterial vaginosis is a common problem for women, with effects ranging from embarrassing and uncomfortable symptoms to serious infections, infertility, and adverse pregnancy outcomes. Currently available treatments, both oral and vaginal, have limited effectiveness and the condition is highly recurrent. Other available vaginal treatments also may require multiple applications, are messy and leak, may not be compatible with condoms, and have unpleasant side effects.

A new single-dose 2% clindamycin vaginal gel resulted in bacterial vaginosis clinical cure rate of 70%, including in women with recurrent disease, with excellent safety. These outcomes were achieved in a population representative of women with bacterial vaginosis, including recurrent bacterial vaginosis, in a double-blind placebo-controlled study conducted in a population that met all four Amsel's criteria and Nugent score criteria for bacterial vaginosis and was culture-negative for *Candida* species.

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Authors' Data Sharing Statement

Will individual deidentified participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Topline study results have been provided on* ClinicalTrials.gov.

What other documents will be available? *Study protocol and the statistical analysis plan have been provided on* ClinicalTrials.gov.

When will data be available (start and end dates)? *The above-mentioned items are currently available.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *The above-mentioned items are available publicly.*

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