Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215650
Priority or standard	Priority
Submit date(s)	6/7/2021
Received date(s)	6/7/2021
PDUFA goal date	12/7/2021
Division/office	Division of Anti-Infectives (DAI)
Review completion date	12/3/2021
Established/proper name	Clindamycin phosphate vaginal gel
(Proposed) proprietary name	Xaciato
Pharmacologic class	Lincosamide
Code name	DARE-BV1
Applicant	Daré Biosciences, Inc.
Dosage form(s)/formulation(s)	Vaginal gel
Dosing regimen	Single dose
Applicant proposed indication(s)/ population(s)	Treatment of bacterial vaginosis in adult women
Proposed SNOMED indication	Bacterial vaginosis (419760006)
Regulatory action	Approval
Approved dosage (if applicable)	Single dose
Approved indication(s)/ population(s) (if applicable)	Treatment of bacterial vaginosis in female patients 12 years of age and older
Approved SNOMED term for indication (if applicable)	Bacterial vaginosis (419760006)

Abbreviations: NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SNOMED, Systematized Nomenclature for Medicine

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Glossary

AE	adverse event
AUC	area under the concentration-time curve
BV	bacterial vaginosis
CDI	*Clostridioides difficile* infection
C_{max}	maximum plasma concentration
GD	gestation day
HEC	hydroxyethyl cellulose
IBD	inflammatory bowel disease
IND	investigational new drug
iPSP	initial Pediatric Study Plan
ITT	intent-to-treat
IV	intravenous
KOH	potassium hydroxide
LD	listed drug
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
NDA	new drug application
PK	pharmacokinetic
PP	per protocol
QD	once daily
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TOC	test-of-cure
w/w	weight per weight

I. Executive Summary

1. Summary of Regulatory Action

The new drug application 215650 for Xaciato (clindamycin phosphate vaginal gel), also referred to as clindamycin phosphate vaginal gel, 2%, and DARE-BV1 in this review, was submitted by Daré Biosciences, Inc. Clindamycin, the active ingredient in DARE-BV1, is a lincosamide antibacterial drug that inhibits bacterial protein synthesis by binding to the 23S ribonucleic acid of the 50S subunit of the ribosome. The new drug application was reviewed by the multidisciplinary review team. Each discipline recommended approval, and I, the signatory authority for this application, concur with those recommendations. DARE-BV1 will be approved for the treatment of bacterial vaginosis (BV) in female patients 12 years of age and older.

The Applicant submitted one adequately designed phase 3 trial that provides substantial evidence of efficacy for the approved indication. Because of the available clinical data from previously approved intravaginal clindamycin products, evidence from a single well-designed phase 3 trial was deemed adequate to support the safety and efficacy of DARE-BV1. The available safety data both from the phase 3 trial as well as from the listed drugs show that DARE-BV1 is safe for its intended use. I concur that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance. The overall benefit-risk is favorable, as described in the Benefit-Risk Framework. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Integrated Assessment document and the Product Quality Review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• BV is a common condition in women of childbearing age that results from an altered vaginal microbiome in which there are fewer resident *Lactobacillus* species and more facultative anaerobes (e.g., *Gardnerella vaginalis*, *Prevotella* species, *Atopobium vaginae*, *Mobiluncus* species, *Porphyromonas* spp., etc.). • Formation of polymicrobial biofilm in the vaginal epthelium is implicated in the pathogenesis of BV. • Risk factors for BV include multiple sexual partners, a new sexual partner, presence of STIs, and douching. • Symptoms of BV can range from none to vaginal discharge that is off-white, thin, homogeneous and associated with an unpleasant "fishy" odor. • Gram stain evaluation of vaginal discharge in conjunction with use of the Nugent score is the reference standard laboratory method for diagnosis of BV. • Although Gram stain evaluation is the reference standard, the Amsel criteria are widely used for diagnosis due to ease of use in the clinical setting and include homogenous vaginal discharge, vaginal pH >4.5, positive whiff-amine test, and clue cells on saline wet mount. The presence of three of the four criteria is required for diagnosis of BV. • There are epidemiological associations between BV and adverse health outcomes such as acquisition of STIs including HIV, increased risk of pregnancy complications including preterm delivery, and increased risks of obstetric and gynecologic complications, postgynecological procedures, and recurrence of BV.	BV is a common condition in women of childbearing age, which can be associated with unpleasant symptoms that may negatively impact the person's quality of life. In addition, it is associated with adverse health outcomes such as increased risk of STIs, including HIV acquisition, and pregnancy complications such as preterm birth. An additional approved therapy, particulary a single-dose, locally applied treatment, would be of benefit to patients and clinicians.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• First-line CDC-recommended treatment options for BV include (CDC 2021): – Oral metronidazole × 7 days* – Metronidazole gel × 5 days* – Clindamycin cream × 7 days* • CDC-recommended alternative treatment options include: – Oral clindamycin × 7 days – Clindamycin vaginal ovules × 3 days* – Oral secnidazole (single dose)* – Oral tinidazole × 2 to 5 days* * Treatment options FDA approved for BV.	There are several effective FDA-approved treatment options for BV. However, most options require multiple days of treatment. An effective, single-dose therapy for BV may improve treatment adherence compared to some of the current treatment options. Its intravaginal route of administration will also minimize systemic exposure and potential adverse effects associated with systemically administered antibacterial drugs.
Benefit	• Efficacy of DARE-BV1 for the treatment of BV was established in a single phase 3, randomized, placebo-controlled trial (DARE-BV1-001). • Subjects were randomized 2:1 to either a single dose of DARE-BV1 or placebo gel. • Efficacy was analyzed in the mITT population of 122 subjects in the DARE-BV1 arm and 59 in the placebo arm. • The primary efficacy endpoint was clinical response at the TOC visit. Significantly more DARE-BV1 subjects were clinical cures at TOC compared to placebo subjects (70.5% versus 35.6%, CMH p<0.001). • The results for various subgroups (age, race, history of BV) were consistent with those for the overall population, with higher clinical cure rates for the DARE-BV1-treated subgroups compared with placebo. • The results for clinical cure at the Interim visit, bacteriological cure at the Interim and TOC visits, and therapeutic cure at the Interim and TOC visits showed that statistically significantly greater proportions of subjects were considered a cure in the DARE-BV1 group compared to the placebo group.	The clinical trial design and endpoints of the phase 3 trial were appropriate. The primary efficacy endpoint analysis demonstrated the efficacy of DARE-BV1 versus placebo. Additional efficacy analyses showed consistent results across various subgroups and the secondary endpoints in the phase 3 trial. The phase 3 trial (DARE-BV1-001) demonstrated the efficacy of DARE-BV1 for the treatment of BV. The trial results are further supported by available clinical data from previously approved intravaginal clindamycin products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The primary safety population consisted of 202 subjects with BV enrolled in the phase 3 trial, DARE-BV1-001, who received a single 5-gram dose of DARE-BV1 (clindamycin vaginal gel). • Two listed drugs, clindamycin injection and clindamycin vaginal cream, were relied on for additional supportive safety data. • There were no deaths, SAEs, or adverse discontinuations among subjects who received DARE-BV1. • Vulvovaginal candidiasis was more common among subjects receiving DARE-BV1 (17%) compared to placebo (4%). However, the cases of candidiasis were mild or moderate in severity and most resolved or were resolving by the end of the trial.	The single phase 3 trial in patients with BV together with the safety findings from the listed drugs provided an adequate safety database for the use of a single dose of DARE-BV1 for the treatment of BV. The only identified risk associated with DARE-BV1 in the phase 3 trial was vulvovaginal candidiasis. However, this risk can be adequately addressed through labeling.

Source: Clinical Reviewer.
Abbreviations: BV, bacterial vaginosis; CDC, Centers for Disease Control and Prevention; CMH, Cochran-Mantel-Haenszel; HIV, human immunodeficiency virus; mITT, modified intent-to-treat; SAE, serious adverse event; STI, sexually transmitted infection; TOC, test-of-cure

2.2. Conclusions Regarding Benefit-Risk

BV is a common condition in women of child-bearing age and results from dysbiosis of the vaginal microbiome with a shift from a *Lactobacillus* species-dominant microbiome to one with high bacterial diversity with dominance of anaerobic bacteria. Although most infections are asymptomatic, symptomatic women experience an off-white vaginal discharge and an unpleasant "fishy smell" that may negatively impact their quality of life (Coudray and Madhivanan 2020). In addition, BV is a risk factor for adverse health outcomes, including acquisition of sexually transmitted infections such human immunodeficiency virus, gonorrhea, chlamydia, herpes simplex virus type 2, human papilloma virus, and trichomoniasis (Martin et al. 1999; Cherpes et al. 2003; Wiesenfeld et al. 2003; Myer et al. 2005; Cohen et al. 2012; Balkus et al. 2014; Dahoud et al. 2019) increased risk of preterm delivery in pregnant women with BV (Eschenbach 1989; Flynn et al. 1999; Klebanoff et al. 2005) and increased risk for obstetric and gynecological complications postgynecological procedures (Persson et al. 1996; Soper 2020).

The efficacy of DARE-BV1 was demonstrated in an adequate and well-designed, placebo-controlled phase 3 trial. The primary efficacy endpoint was clinical response at the test-of-cure (TOC) visit. Significantly more DARE-BV1 subjects were clinical cures at TOC compared to placebo subjects (70.5% versus 35.6%, Cochran-Mantel-Haenszel $p<0.001$). In addition, various subgroup analyses (age, race, history of BV) were consistent with those of the overall population, in that clinical cure rates for subjects treated with DARE-BV1 were higher than placebo. The results for clinical cure at the Interim visit, bacteriological cure at the Interim and TOC visits, and therapeutic cure at the Interim and TOC visits showed that statistically significantly greater proportions of subjects were

considered a cure in the DARE-BV1 group as compared to the placebo group. The trial results are supported by available clinical data from previously approved intravaginal clindamycin products.

The safety data from the phase 3 trial are in line with previously observed and anticipated adverse effects of vaginally administered antibacterial products, including other approved intravaginal clindamycin products, such as an increased incidence of vaginal candidiasis and vaginal discomfort. No new safety signals, serious adverse events, or deaths were reported in the DARE-BV1-treated arm.

Although there are several FDA-approved treatments for BV, most are multidose regimens. Hence, a single-dose, locally administered treatment such as DARE-BV1 is a desirable addition to the BV treatment armamentarium. The overall safety and efficacy data render the benefit-risk assessment favorable for approval of DARE-BV1.

II. Interdisciplinary Assessment

3. Introduction

Daré Bioscience seeks approval of Xaciato (clindamycin phosphate vaginal gel), also referred to as clindamycin phosphate vaginal gel, 2%, and DARE-BV1 in this review, as a single dose for the treatment of bacterial vaginosis (BV) in adult women. This new drug application (NDA) is a 505(b)(2) application in which the Applicant relies on two listed drugs, clindamycin phosphate vaginal cream and clindamycin in 0.9% sodium chloride injection. The active drug in DARE-BV1, clindamycin, has been used clinically for many years and has a known safety profile. Clindamycin is a lincosamide antibacterial drug that inhibits bacterial protein synthesis by binding to the 23S ribonucleic acid of the 50S subunit of the ribosome.

Daré Bioscience submitted an investigational new drug application (#143919) for DARE-BV1 on November 15, 2019, for the treatment of BV. FDA granted Qualified Infectious Disease Product and Fact Track Designations on August 7, 2019, and March 4, 2020, respectively. The Applicant conducted a single phase 3, randomized, multicenter, placebo-controlled trial of DARE-BV1 in BV. Refer to Section III.12 for the complete regulatory history.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Definition of Vaginal Discharge Used in Assessing Clinical Cure

- Refer to the discussion in Section 6.3.1.

3.1.1.2. Positive Culture for *Candida* and Nugent Score Cutoff of 7 for Defining the Modified Intent-to-Treat Population

- Refer to the discussion in Section 6.3.2.

3.1.1.3. Potential Role of [redacted] (b) (4)

- Refer to the discussion in Section 6.3.3.

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Safety in Females 12 to <18 Years of Age

- Only one subject <18 years of age was enrolled in the phase 3 study. Refer to the discussion in Section 7.7.1.

3.2. Approach to the Review

The efficacy and safety of DARE-BV1 for the treatment of BV were primarily assessed using the data from Trial DARE-BV-001 (Table 3). DARE-BV-001 was designed appropriately, followed FDA's Guidance for Industry: *Bacterial Vaginosis: Developing Drugs for Treatment*,[1] and is fit for purpose. The efficacy and safety findings for DARE-BV1 were supplemented by data on two listed drugs, clindamycin phosphate in sodium chloride injection and Cleocin (clindamycin phosphate) vaginal cream.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for DARE-BV1

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints[2]	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
DARE-BV1-001 (NCT04370548)	Adults and adolescents with bacterial vaginosis	Control type: Placebo controlled Randomization: 2:1 randomization Blinding: Investigator, subject blinding Biomarkers: N/A Innovative design features: N/A	Drug: DARE-BV1 (clindamycin phosphate vaginal gel, 2%) Dosage: 5 g Number treated: 202 Duration (quantity and units): Single dose Choose time unit. Drug: Placebo gel Dosage: 5 g Number treated: 103 Duration (quantity and units): Single dose	Primary: Clinical cure at test-of-cure visit (Day 21-30) Secondary: Clinical cure at the interim assessment visit (Day 7-14).	307 (204 randomized to DARE-BV1; 103 randomized to placebo)	35 centers in the United States

Source: Reviewer.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] Clinical cure was defined as resolution of abnormal vaginal discharge associated with BV, negative 10% KOH "whiff test", and clue cells <20% of the total epithelial cells in a saline wet mount.
Abbreviations: BV, bacterial vaginosis; KOH, potassium hydroxide; N/A, not applicable; NCT, National Clinical Trial

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	6.2.1.3 Resolution of abnormal vaginal discharge was noted by the clinician/investigator
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The clinical pharmacologic properties of DARE-BV1 were evaluated in one clinical pharmacokinetic study, which demonstrated low systemic clindamycin exposure (Table 5).

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Xaciato vaginal gel contains clindamycin phosphate, a lincosamide semisynthetic antibacterial.
Mechanism of action	Clindamycin inhibits bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome. Clindamycin is predominantly bacteriostatic. Although clindamycin phosphate is inactive in vitro, rapid in vivo hydrolysis converts it to active clindamycin.
Active moieties	Clindamycin
QT interval prolongation	N/A (local acting drug)
	General Information
Bioanalysis	A validated HPLC/MS/MS method was used to determine the concentrations of clindamycin in human plasma.
Healthy subjects versus patients	Systemic PK is similar in healthy women and women with bacterial vaginosis.
Drug exposure after single dosage	**Table 6. Single-Dose Pharmacokinetics**

Parameter	Clindamycin[a] Mean (CV%)	n
C_{max} (ng/mL)	69.2 (113)	21
AUC_{0-t} (h·ng/mL)	1179 (85.1)	21
AUC_{0-24}	818 (112)	21
AUC_{inf}	1975 (53.2)	9

Source: Study report DARE-BV1-PK1.
[a] Based on pharmacokinetic analyses in healthy female subjects receiving a single dose of DARE-BV1 (Study DARE-BV1-PK1). In the study, 22 subjects were enrolled and 21 were dosed.
Abbreviations: AUC_{0-24}, area under the concentration-time curve from 0-24 hours; AUC_{0-t}, area under the concentration-time curve from time zero to time t; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum concentration; CV, coefficient of variation; n, number of samples

Range of effective dosage(s) or exposure	N/A (local acting drug)
Maximally tolerated dosage or exposure	N/A (local acting drug)

Characteristic	Drug Information
Dosage proportionality	N/A (local acting drug)
Accumulation	N/A (local acting drug)
Time to achieve steady-state	N/A (local acting drug)
Bridge between to-be-marketed and clinical trial formulations	The formulation of DARE-BV1 used in the clinical pharmacokinetic study is the to-be-marketed formulation.
	Absorption
Bioavailability	N/A (local acting drug)
T_{max}	The median (range) t_{max} occurred at 6.00 hours (4 to 96 hours).
Food effect (fed/fasted); geometric least-squares mean and 90% CI	N/A (local acting drug)
	Distribution
Volume of distribution	N/A (local acting drug)
Plasma protein binding	N/A (local acting drug)
Drug as substrate of transporters	N/A (local acting drug)
	Elimination
Mass balance results	N/A (local acting drug)
Clearance	N/A (local acting drug)
Half-life[1]	20 hours (CV 151%)
Metabolic pathway(s)	N/A (local acting drug)
Primary excretion pathways (% dosage)	N/A (local acting drug)
	Intrinsic Factors and Specific Populations
Body weight	N/A (local acting drug)
Age	N/A (local acting drug)
Renal impairment	N/A (local acting drug)
Hepatic impairment	N/A (local acting drug)

Characteristic	Drug Information
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	N/A (local acting drug)
Inhibition/induction of transporter systems	N/A (local acting drug)

Source: Study report DARE-BV1-PK1 and Xaciato™ (clindamycin phosphate) Vaginal Gel (b) (4).
[1] Of 21 dosed subjects, half-life was reported from 10 subjects. The subjects with adjusted R^2 <0.8 or <3 points in the elimination phase were not reported based on the study report (DARE-BV1-PK1). Per the labeling of Clindamycin Phosphate in 0.9% Sodium Chloride Injection (NDA 208083), the average serum elimination half-life of active clindamycin is about 3 hours in adult and 2.5 hours in pediatric patients. Based on the vaginal PK data in Study DARE-BV1-PK1, the reviewer estimated the half-life of vaginal clindamycin to be around 25.98 hours. Therefore, clindamycin gel's systemic half-life is closer to the vaginal absorption half-life rather than the half-life of IV injection, indicating that the long systemic half-life of clindamycin might be caused by slow vaginal absorption.
Abbreviations: CI, confidence interval; CV, coefficient of variation; HPLC/MS/MS, high-performance liquid chromatography with tandem mass spectrometry; IV, intravenous; N/A, not applicable; NDA, new drug application; PK, pharmacokinetic; RNA, r bonucleic acid; T_{max}, time to maximum concentration

5.1. Nonclinical Assessment of Potential Effectiveness

Microbiological Studies

Clindamycin showed an in vitro minimum inhibitory concentration (MIC) of 0.015 to >16 µg/mL and a concentration that inhibits bacterial growth by 90% of 0.12 to 16 µg/mL against 507 anaerobic species (of which 401 were of the *Bacteroides fragilis* Group) (Aldridge et al. 2001).

The clindamycin MIC against bacteria associated with BV (*Bacteroides fragilis* Group, *Prevotella* spp., *Peptostreptococcus* spp., and *Fusobacterium* spp.) ranged from <0.03 to >128 µg/mL (Rezanka et al. 2007).

The MICs of 12 isolates of *Atopobium vaginae* were <0.016 µg/mL and the concentration that inhibits bacterial growth by 90% was 0.015 µg/mL. Additionally, four isolates of *Gardnerella vaginalis* had an MIC range of <0.016 to 0.047 µg/mL (De Backer et al. 2006).

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The dose in DARE-BV1-001 and of the to-be-marketed product (5-gram vaginal gel containing 100 mg of clindamycin) is identical to the reference listed drug (Cleocin cream).

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial DARE-BV1-001

6.2.1.1. Design, DARE-BV1-001

DARE-BV1-001 was a multicenter, randomized placebo-controlled trial of a single dose of DARE-BV1 compared to placebo vaginal gel (hydroxyethyl cellulose Universal Placebo Gel) for the treatment of BV. The overall design followed the recommendations provided in FDA's Guidance for Industry: *Bacterial Vaginosis: Developing Drugs for Treatment*.

Eligible subjects were randomized in a 2:1 ratio to either a single 5 g dose of clindamycin phosphate vaginal gel, 2% (DARE-BV1) or a single 5 g dose of placebo vaginal gel. The trial was stratified by study site and race (African American or not African American). Study drug was applied intravaginally within 1 day of randomization. Subjects were evaluated at three timepoints: Day 1 screening/randomization visit, Day 7 to 14 interim assessment visit, and Day 21 to 30 test-of-cure (TOC) visit. See the protocol synopsis in Section III.15 for more details on the study design.

6.2.1.2. Eligibility Criteria, DARE-BV1-001

Eligible subjects included females aged 12 years and older with a clinical diagnosis of BV. A clinical diagnosis of BV was defined as the presence of an off-white (milky or gray), thin,

homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina; the presence of clue cells >20% of the total epithelial cells on microscopic examination of a saline wet mount; vaginal secretion pH of >4.5; and a fishy odor of the vaginal discharge upon addition of a drop of 10% potassium hydroxide (i.e., a positive whiff test). Subjects were excluded if they had an active vulvovaginitis or other active infectious causes of cervicitis, vaginitis, or vulvitis, based on the results of the thorough clinical assessments and in-clinic microscopic assessments performed prior to enrollment (e.g., candidiasis, *T. vaginalis*, *C. trachomatis*, *N. gonorrhoeae*, or genital lesions or ulcers consistent with human papillomavirus, herpes simplex virus, syphilis, chancroid, etc.); had any vaginal, vulvar, or genitourinary condition that, according to the investigator's judgment, could confound the interpretation of clinical response; or were currently receiving or had received antifungal or antibacterial therapy (systemic or intravaginal) within 14 days of the screening/randomization visit.

6.2.1.3. Statistical Analysis Plan, DARE-BV1-001

Analysis Populations

- Intent-to-treat (ITT): The ITT population included all randomized subjects.
- Safety: The safety population included all ITT population subjects who applied study drug.
- Modified ITT (mITT): The mITT population included all safety population patients except those excluded for: (1) a positive test result for other concomitant vaginal or cervical infections at baseline (e.g., *T. vaginalis*, *N. gonorrhoeae*, *C. trachomatis*, *Candida* spp.); (2) a baseline Nugent score of <7; or (3) a missing baseline score.
- Per protocol: The per protocol population included patients from the mITT population who either received other BV therapy during the study for any reason or met the following criteria: (1) met all four Amsel's criteria at screening, (2) applied study drug within 1 day of randomization, (3) did not use a prohibited medication prior to the Day 21 to 30 visit, (4) attended the Day 21 to 30 visit, and (5) had no other major protocol violations that impacted the primary or secondary endpoints. Subjects were also excluded if they did not receive the treatment to which they were randomized.

The primary efficacy analysis population was the mITT population and is the focus of the efficacy review. For the ITT and mITT populations, subjects were analyzed according to the treatment to which they were randomized. For the Safety population, subjects were analyzed according to the treatment received.

Analysis Methods

The primary efficacy endpoint was the proportion of subjects with a clinical cure at the TOC (Day 21 to 30) visit. Clinical cure was defined as absence of the abnormal discharge consistent with BV, a negative whiff test, and clue cells <20% of total epithelial cells in a saline wet mount. Subjects who received other BV therapy for any reason or any non-study treatment that could interfere with the assessment of the subject's BV were included in the analysis as treatment failures for all visits on or after receipt of the other BV therapy or non-study treatment.

Reviewer's Comment: *In FDA's Guidance for Industry,* Bacterial Vaginosis: Developing Drugs for Treatment*, the definition of clinical cure states resolution of abnormal discharge with the*

intention of meaning absence of all abnormal discharge and not just an abnormal discharge consistent with BV, as used by the Applicant. Refer to Section 6.3.1 for further discussion.

A Cochran-Mantel-Haenszel test stratified by study site and race (African American/black versus all others) was performed. If the p-value from the Cochran-Mantel-Haenszel (general association) chi-squared test was ≤0.05, then the null hypothesis that the clinical cure rates in the DARE-BV1 and placebo groups were equal was rejected. A 95% confidence interval, using Yates' correction, for the difference (DARE-BV1 versus placebo) in the proportion of patients achieving clinical cure was also calculated.

Key secondary endpoints included clinical cure at the Interim visit (Day 7 to 10), bacteriological cure at the TOC visit, therapeutic cure at the TOC visit, bacteriological cure at the Interim visit, and therapeutic cure at the Interim visit. Bacteriological cure was defined as a Nugent score <4. Therapeutic cure was defined as both a clinical cure and bacteriological cure.

Analysis of the secondary endpoints followed the same method as the primary endpoint. Statistical testing of the secondary efficacy endpoints was only performed if the p-value for the primary endpoint was ≤0.05. Hypothesis testing for the secondary efficacy endpoints was conducted in a sequential manner in the order stated above to control the Type 1 error rate.

Sample Size Calculation

Assuming the clinical cure rates were 55% for DARE-BV1 and 30% for placebo, and 35% of randomized subjects would not be in the mITT population, a sample size of 188 DARE-BV1 subjects and 94 placebo subjects would have 90% power to detect a difference between the treatment groups with a two-sided significance level of 0.05.

6.2.1.4. Results of Analyses, DARE-BV1-001

Patient Disposition

The study was initiated on July 9, 2020 and was completed on November 12, 2020. It was conducted at 35 sites (32 enrolled subjects) in the United States. A total of 513 subjects was screened, 307 of whom were randomized. The most common reason for screening failure was due to not having a clinical diagnosis of BV.

Table 7. Patient Screening and Randomization, DARE-BV1-001

Disposition	Number
Number of patients screened	513
Number of screening failures	206
Number of patients randomized	307

Source: Table 10-1 of the DARE-BV1-001 clinical study report.

Subject disposition is summarized in Table 8. Of the 307 randomized subjects (ITT population), 204 were randomized to DARE-BV1 and 103 were randomized to placebo. All but one subject, randomized to DARE-BV1, applied assigned study drug and are included in the Safety population. The mITT population included 122 (59.8%) DARE-BV1 subjects and 59 (57.3%) placebo subjects. For a discussion of the reasons for exclusion from the mITT population, refer to Section 3.1.1.2. The per protocol population excluded an additional 20 DARE-BV1 subjects and 12 placebo subjects, primarily because of protocol deviations.

The majority of the subjects completed the study (Table 8). Although the study discontinuation rate was low, a higher percentage of subjects in the DARE-BV1 arm (6.9%) compared to the placebo arm (2.9%) discontinued the study early. The reasons for early discontinuation were primarily loss to follow-up and withdrawal of consent.

Table 8. Subject Disposition, DARE-BV1-001

Disposition Category	DARE-BV1 N=204 n (%)	Placebo N=103 n (%)
Subjects randomized/ ITT population	204 (100.0)	103 (100.0)
mITT population	122 (59.8)	59 (57.3)
Per protocol population	102 (50.0)	47 (45.6)
Safety population	203 (99.5)	103 (100.0)
Discontinued study	14 (6.9)	3 (2.9)
Lost to follow-up	7 (3.4)	2 (1.9)
Withdrawal of consent by subject	6 (2.9)	1 (1.0)
Other	1 (0.5)	0 (0)

Source: Reviewer-conducted analysis using the ADSL dataset.
Abbreviation: ITT, intent-to-treat, mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with indicated disposition

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics of the ITT population are presented in Section III.16. Table 9 summarizes the baseline demographic and clinical characteristics of the mITT population. The median age was 34 years. The majority of the subjects in the mITT population was black/African American (61.4%). This was a slightly larger proportion than in the ITT population (56%). There was a higher percentage of Hispanic subjects in the DARE-BV1 arm (29.5%) than in the placebo arm (15.3%). Per the definition of the mITT population, all subjects had a baseline Nugent score between 7 and 10. Approximately 89% of subjects reported having a history of BV in their lifetime, and approximately 18% of subjects reported having more than three BV episodes in the past 12 months.

Table 9. Baseline Demographic and Clinical Characteristics, mITT Population, DARE-BV1-001

Characteristic	DARE-BV1 (N=122)	Placebo (N=59)
Sex, n (%)		
Female	122 (100.0)	59 (100.0)
Age, years		
Mean (SD)	34.1 (8.4)	34.9 (8.7)
Median (minimum, maximum)	34 (15, 56)	34 (23, 59)
Age groups (years), n (%)		
≤20	4 (3.3)	0 (0)
21 to 30	38 (31.1)	20 (33.9)
31 to 40	55 (45.1)	28 (47.5)
41 to 50	21 (17.2)	6 (10.2)
≥51	4 (3.3)	5 (8.5)
Race, n (%)		
White	40 (32.8)	21 (35.6)
Black/African American	80 (65.6)	36 (61.0)
Other	2 (1.6)	2 (3.4)
Ethnicity, n (%)		
Hispanic	36 (29.5)	9 (15.3)
Non-Hispanic	85 (69.7)	50 (84.7)
Nugent score, n (%)		
7 to 10	122 (100.0)	59 (100.0)
History of BV, n (%)		
Yes	111 (91.0)	50 (84.8)
No	11 (9.0)	9 (15.3)
Episodes in past 12 months, n (%)		
≤3	101 (82.8)	46 (78.0)
>3	20 (16.4)	13 (22.0)
History, but number not reported	1 (0.8)	0 (0)

Source: Reviewer-conducted analyses using the ADSL, ADMB, and ADFA datasets.
Abbreviations: BV, bacterial vaginosis; mITT, modified intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Primary Endpoint

Clinical response at the TOC visit for the mITT population is summarized in Table 10. Significantly more DARE-BV1 subjects were a clinical cure at TOC compared to placebo subjects (70.5% versus 35.6%, Cochran-Mantel-Haenszel $p<0.001$). Most subjects were considered a failure because at least one of the three criteria needed for cure was not met. A higher percentage of placebo subjects than DARE-BV1 subjects was considered a failure because they received additional BV medication at or before the TOC visit. Although missing data were minimal, there were more DARE-BV1 subjects than placebo subjects with missing data. These subjects were treated as failures in the analysis. For discussions on the impact of the abnormal vaginal discharge definition and the definition of the mITT population on the assessment of clinical cure at TOC, refer to Sections 6.3.1 and 6.3.2, respectively.

Table 10. Clinical Response at Test-of-Cure Visit (Day 21 to 30), mITT Population, DARE-BV1-001

Response	DARE-BV1 (N=122)	Placebo (N=59)	Difference (95% CI)[1] p-Value[2]
Cure, n (%)	86 (70.5)	21 (35.6)	34.9 (19.0, 50.8) <0.001
Failure, n (%)	36 (29.5)	38 (64.4)	
At least one criterion not met	26 (21.3)	29 (49.2)	
Received additional BV medication at or before TOC	2 (1.6)	8 (13.6)	
Missing	8 (6.6)	1 (1.7)	

Source: Reviewer-conducted analysis using the ADEFF and ADFA datasets.
[1] Difference is DARE-BV1 minus placebo and 95% confidence interval.
[2] p-value from CMH test adjusted for study site and race (black/African American versus all others).
Abbreviations: BV, bacterial vaginosis; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with the indicated response; TOC, test-of-cure

Subgroup analyses for clinical cure at TOC in the mITT population are presented in Table 11. The results for the various subgroups were consistent with those seen for the overall population in that clinical cure rates for the DARE-BV1-treated groups were higher than placebo. However, the treatment effect for black subjects was smaller than that for white subjects. The single adolescent (15 years) enrolled in the study who received DARE-BV1 was a clinical cure at TOC. Irrespective of the number of BV episodes in the past 12 months, the clinical cure rates among DARE-BV1 subjects in both subgroups were similar.

Table 11. Subgroup Analyses of Clinical Cure at Test-of-Cure Visit (Day 21 to 30), mITT Population, DARE-BV1-001

Characteristic	DARE-BV1 (N=122)	Placebo (N=59)	Difference (95% CI)[1]
Race, n (%)			
Black	50 of 80 (62.5)	14 of 36 (38.9)	23.6 (2.5, 44.8)
White	34 of 40 (85.0)	7 of 21 (33.3)	51.7 (25.0, 78.3)
Other	2 of 2 (100)	0 of 2 (0)	-
Age, n (%)			
<35 years	43 of 62 (69.4)	11 of 31 (35.5)	33.9 (11.1, 56.7)
≥35 years	43 of 60 (71.7)	10 of 28 (35.7)	36.0 (12.2, 60.0)
History of BV, n (%)			
Yes	79 of 111 (71.2)	17 of 50 (34.0)	37.2 (20.1, 54.2)
No	7 of 11 (63.6)	4 of 9 (44.4)	19.2 (-34.1, 72.4)
Episodes in past 12 months, n (%)			
≤3	72 of 101 (71.3)	18 of 46 (39.1)	32.2 (13.9, 50.4)
>3	14 of 20 (70.0)	3 of 13 (23.1)	46.9 (10.1, 83.7)
Unknown	0 of 1 (0)	-	-

Source: Reviewer-conducted analysis using the ADEFF and ADFA datasets.
[1] Difference is DARE-BV1 minus placebo and 95% confidence interval.
Abbreviations: BV, bacterial vaginosis; CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with the indicated characteristic

In the mITT population, 11 DARE-BV1 subjects and 6 placebo subjects had tube weight differences of study drug of >10.5 g, suggesting that two or more doses were expelled. The clinical cure at TOC visit results excluding these subjects are as follows: 77 of 111 (69.4%) for DARE-BV1 and 18 of 53 (34.0%) for placebo, for a difference of 35.4%. These results are similar to the overall population, suggesting that the subjects who may have received additional doses of the study drug had a minimal effect on the efficacy results.

Secondary Endpoints

The results for clinical cure at the Interim visit, bacteriological cure at the Interim and TOC visits, and therapeutic cure at the Interim and TOC visits are summarized for the mITT population in Table 12. For each of the secondary endpoints, a statistically significant greater proportion of subjects was considered a cure in the DARE-BV1 group as compared to the placebo group, providing further support for the efficacy of DARE-BV1.

Table 12. Secondary Endpoints, mITT Population, DARE-BV1-001

Endpoint, n (%)	DARE-BV1 (N=122)	Placebo (N=59)	Difference (95% CI)[1] p-Value[2]
Clinical cure at Interim visit	93 (76.2)	14 (23.7)	52.5 (38.0, 67.0) <0.001
Bacteriological cure at TOC visit	53 (43.4)	3 (5.1)	38.4 (26.7, 50.1) <0.001
Bacteriological cure at Interim visit	50 (41.0)	2 (3.4)	37.6 (26.5, 48.7) <0.001
Therapeutic cure at TOC visit	45 (36.9)	3 (5.1)	31.8 (20.3, 43.3) <0.001
Therapeutic cure at Interim visit	43 (35.2)	0 (0)	35.2 (25.5, 45.0) <0.001

Source: Reviewer-conducted analysis using the ADEFF dataset.
[1] Difference is DARE-BV1 minus placebo and 95% confidence interval.
[2] p-Value by CMH test adjusted for study site and race (black/African American versus all others).
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with the indicated endpoint; TOC, test-of-cure

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Definition of Vaginal Discharge Used in Assessing Clinical Cure

Issue

Assessment of the definition of vaginal discharge used to define clinical cure in the phase 3 DARE-BV1-001 trial.

Background

FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*, recommends clinical cure be defined as resolution of the abnormal discharge, a negative whiff test, and the presence of clue cells at less than 20% of the total epithelial cells on microscopic examination of a saline wet mount. With respect to resolution of abnormal discharge, the intent was to imply return to a normal discharge and not merely resolution of the abnormal discharge associated with BV. The reasoning behind this was based on concern over the ability of investigators to consistently differentiate the cause of an abnormal discharge and whether trading one abnormal discharge for another was indicative of an acceptable clinical response.

After consulting experts, the Applicant indicated that defining normal physiological discharge is challenging because it can have a broad range of appearances but does not look like the discharge of women with BV. Therefore, the definition of clinical cure used in the study was

absence of the abnormal vaginal discharge associated with BV, negative whiff test, and the presence of <20% clue cells. The case report form recorded information on vaginal discharge as normal, abnormal (consistent with BV), abnormal (consistent with candidiasis), or abnormal (other). This enabled sensitivity analyses to be conducted, as recommended by the clinical review team, in which subjects with any abnormal discharge could be considered failures.

Assessment

Table 13 summarizes the classification of vaginal discharge at the TOC visit for the mITT population. For both treatment arms, the majority of the abnormal discharge present at TOC was classified as abnormal (consistent with BV). Two of the DARE-BV1 subjects and two of the placebo subjects with an abnormal (other) discharge and the placebo subject with abnormal (consistent with candidiasis) discharge were considered clinical failures at TOC in the primary analysis due to clue cells ≥20% and/or a positive whiff test or receipt of additional BV treatment. The remaining eight DARE-BV1 subjects and one placebo subject with an abnormal discharge other than one consistent with BV were considered clinical cures in the primary analysis. Subjects with missing data were imputed as failures. However, of the 10 subjects with missing vaginal discharge, 1 DARE-BV1 subject and 2 placebo subjects were considered clinical failures because they received additional BV medication at or before the TOC visit.

Table 13. Vaginal Discharge at TOC, mITT Population, DARE-BV1-001

Discharge Parameter, n (%)	DARE-BV1 (N=122)	Placebo (N=59)
Normal	88 (72.1)	31 (52.5)
Abnormal (consistent with BV)	17 (13.9)	21 (35.6)
Abnormal (consistent with candidiasis)	4 (3.3)	1 (1.7)
Abnormal (other)	6 (4.9)	3 (5.1)
Missing	7 (5.7)	3 (5.1)

Source: Reviewer-conducted analysis using the ADFA dataset.
Abbreviations: BV, bacterial vaginosis; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with indicated parameter; TOC, test-of-cure

Table 14 summarizes the results of the primary analysis of clinical cure at TOC as well as the sensitivity analysis that treats a subject with any abnormal discharge as a failure. The difference in the clinical cure rates between treatment groups is reduced by about 5% when any discharge is considered a failure. However, there is no change in the overall conclusion, i.e., the rate of clinical cure with DARE-BV1 treatment is significantly higher than with placebo.

Table 14. Sensitivity Analysis of Clinical Cure at the Test-of-Cure Visit, mITT Population, DARE-BV1-001

Failure if Discharge is	DARE-BV1 (N=122)	Placebo (N=59)	Difference (95% CI)[1]
Abnormal (consistent with BV)[2]	86 (70.5)	21 (35.6)	34.9 (19.0, 50.8)
Any abnormal	78 (63.9)	20 (33.9)	30.0 (14.0, 46.0)

Source: Reviewer-conducted analysis using the ADEFF and ADFA datasets.
[1] Difference is DARE-BV1 minus placebo and 95% confidence interval.
[2] Protocol definition for primary endpoint/analysis.
Abbreviations: BV, bacterial vaginosis; CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with the indicated failure

Conclusion

The overall results are robust to vaginal discharge criteria when defining clinical cure. Therefore, there is no concern regarding the interpretation of the efficacy of DARE-BV1 based on the protocol definition of clinical cure. However, since this definition is different from that used in prior BV treatment studies and that in FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*, it is recommended when presenting the results of the study in the Clinical Studies section of the product labeling that the definition of clinical cure be clearly stated.

6.3.2. Positive Culture for *Candida* and Nugent Score Cutoff of 7 for Defining the Modified Intent-to-Treat Population

Issue

Assessment of positive culture for *Candida* and a Nugent score cutoff of 7 at baseline for defining the mITT population in the phase 3 DARE-BV1-001 trial.

Background

The mITT population in the protocol was defined as all treated subjects excluding those demonstrating a positive test result for other concomitant vaginal or cervical infections at baseline (e.g., *T. vaginalis*, *N. gonorrhoeae*, *C. trachomatis*, and *Candida* spp.) or who were determined to have a baseline Nugent score <7 or if the baseline score was missing. This definition differs from that used in previous BV treatment studies in two regards:

1. This is the first study conducted under FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*, which recommends a Nugent score cut-off of 7 rather than 4.
2. Previous studies did not require baseline culture testing for *Candida.* Saline and potassium hydroxide wet mount were considered acceptable microscopic assessments for ruling out vaginal candidiasis at baseline. The Applicant indicated that confirming the presence of BV and ruling out the presence of other infectious and noninfectious causes of vulvovaginitis is important for ensuring enrollment of a population with BV only. Since the medical literature suggests that clinical and microscopic assessments are less than optimal for identifying patients with candidiasis, the protocol also required a vaginal culture for *Candida* spp. to be obtained at baseline from each subject and used it to determine if the patient could be included in the mITT population.

Although both of these criteria increase the likelihood of enrolling a population with BV only, it is of interest to determine the impact of this definition of the mITT population on interpretation of the efficacy results.

Assessment

Table 15 lists the various mITT populations that will be assessed and the reasons for exclusion from those populations. The mITT1 population follows the protocol definition. The mITT2

population follows that recommended in FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*. The mITT4 population is consistent with previous BV studies conducted prior to FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*. The mITT3 population uses the previous Nugent score cutoff of <4 with the added requirement of a positive *Candida* culture result.

Table 15. mITT Population Definitions

Reason for Exclusion	mITT1	mITT2	mITT3	mITT4
Nugent score				
<4 or missing			X	X
<7 or missing	X	X		
Positive sexually transmitted infection result	X	X	X	X
Positive *Candida* culture	X		X	

Source: Reviewer.
Abbreviation: mITT, modified intent-to-treat

The reasons for exclusion from the protocol-defined mITT population (referred to as mITT1) are summarized in Table 16. The last three rows of the table denote the additional subjects excluded from the population who would not have been excluded based on the definition in prior studies. The majority of these subjects were excluded for a positive *Candida* culture only. Table 16 also indicates the subjects included in the other defined mITT populations.

Table 16. Reasons for Exclusion From the mITT Populations, DARE-BV1-001

Reason for Exclusion From mITT1, n (%)	DARE-BV1 (N=122)	Placebo (N=59)	Include in mITT2	Include in mITT3	Include in mITT4
Not treated	1 (0.5)	-			
Nugent <4 only	14 (6.9)	10 (9.7)			
Nugent <4 and positive *Candida* culture	2 (1.0)	2 (1.9)			
Nugent 4 to 6 and STI	1 (0.5)	-			
STI and positive *Candida* culture	3 (1.5)	-			
STI only	5 (2.5)	2 (1.9)			
Nugent 4 to 6 and positive *Candida* culture	3 (1.5)	2 (1.9)			Yes
Nugent 4 to 6 only	19 (9.3)	13 (12.6)		Yes	Yes
Positive *Candida* culture only	34 (16.7)	15 (14.6)	Yes		Yes

Source: Reviewer-conducted analysis using the ADSL and ADMB datasets.
Abbreviations: mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects with indicated exclusion reason; STI, sexually transmitted infection

Clinical cure at TOC for the various mITT populations is summarized in Table 17. Overall, the results are robust to the various definitions of the mITT population. When comparing mITT populations that used different Nugent criteria (mITT1 versus mITT3 and mITT2 versus mITT4), there is little difference in the DARE-BV1 response rates, but the placebo rates are about 2% higher with the less-restrictive Nugent exclusion criterion. When comparing populations that use different *Candida* culture criteria (mITT1 versus mITT2 and mITT3 versus mITT4), the response rates are slightly higher in both treatment groups when subjects with a positive *Candida* culture are excluded.

Table 17. Clinical Cure at Test-of-Cure Visit for the mITT Populations, DARE-BV1-001

Subjects With Clinical Cure in mITT Population	DARE-BV1	Placebo	Difference (95% CI)[1]
mITT1, n/N (%) excludes Nugent <7, STI, or positive *Candida* culture	86 of 122 (70.5)	21 of 59 (35.6)	34.9 (19.0, 50.8)
mITT2, n/N (%) excludes Nugent <7 or STI	107 of 156 (68.6)	24 of 74 (32.4)	36.2 (22.3, 50.1)
mITT3, n/N (%) excludes Nugent <4, STI, or positive *Candida* culture	100 of 141 (70.9)	27 of 72 (37.5)	33.4 (18.9, 47.9)
mITT4, n/N (%) excludes Nugent <4 or STI	122 of 178 (68.5)	31 of 89 (34.8)	33.7 (20.8, 46.6)

Source: Reviewer-conducted analysis using the ADEFF and ADMB datasets.
[1] Difference is DARE-BV1 minus placebo and 95% confidence interval.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, number of subjects in mITT population; n, number of subjects with clinical cure; STI, sexually transmitted infection

Conclusion

The overall results are robust to the definition of the mITT population. Therefore, there is no concern regarding interpretation of the efficacy of DARE-BV1 based on the protocol definition of the mITT population. However, since this definition is different from that used in past BV treatment studies, it is recommended when presenting the results of the study in the Clinical Studies section of the product labeling that the definition of the mITT population be clearly stated.

6.3.3. Potential Role of Citric Acid as an Active Antibacterial Component

Citric acid monohydrate and sodium citrate dihydrate are present at (b) (4)% weight per weight (w/w) and (b) (4)% w/w, respectively, in a 5-gram dose of DARE-BV1, totaling to (b) (4)% citric acid in the drug product. The Applicant stated these components were inactive ingredients used (b) (4). The review team raised the issue of citrate compounds potentially contributing to the antimicrobial activity of DARE-BV1. Some publications were identified in the literature that showed antimicrobial activity of citrate-containing products against gram-negative pathogens (Weijmer et al. 2002; Burel et al. 2021).

The placebo (hydroxyethyl cellulose) arm in the phase 3 trial did not contain citric acid; hence, if citric acid has antimicrobial properties at the pH and concentration that is present in DARE-BV1, DARE-BV1 would be considered a combination product, and the Applicant would need to demonstrate the contribution of each active component, namely, citric acid and clindamycin to DARE-BV1.

The Agency requested that the Applicant provide available data, either scientific publications or any additional nonclinical data they may have to elucidate the activity of citric acid and sodium citrate, alone and in combination against pathogens associated with BV at concentrations similar to DARE-BV1. The Applicant noted that they did not have nonclinical data evaluating the potential antimicrobial activity of the two citrate compounds alone or in combination. The Applicant also stated that although boric acid and lactic acid have been studied for treatment/prevention of BV, there were no clinical data regarding use of products containing citric acid as a sole active ingredient for treatment of BV.

The Applicant noted that the FDA-approved contraceptive gel, Phexxi (also known as EVO100, Acidform and Amphora), contains (b) (4) citric acid (1% w/w) (b) (4) Of note, in addition to citric acid, Phexxi contains lactic acid (1.8% w/w) and potassium bitartrate (0.4% w/w). A publication reported the result of a small, randomized, controlled trial in nonpregnant women where subjects received either Acidform (n=13) or 10% metronidazole gel for 5 days for the treatment of symptomatic BV and found that at Day 7 to 12 after completion of treatment, 10 of the 13 subjects in the Acidform arm (77%) and 2 of the 17 in the metronidazole (12%) arm were considered treatment failures. Of the 3 subjects in the Acidform arm who were deemed clinical successes at the first visit, 2 had recurrence by the follow-up visit at Day 28 to 35 after completion of treatment as compared to 6 of 15 subjects in the metronidazole arm. In this small trial the authors concluded that "Acidform gel was significantly less effective than high-dose metronidazole gel for the treatment of symptomatic BV…these results increase the doubts already raised with respect to any actual benefit of using intravaginal acidification as a feasible alternative for the treatment of symptomatic BV" (Simoes et al. 2006).

Phexxi's registrational trial, AMP001, compared Phexxi with Conceptrol (also known as nonoxynol-9) (Barnhart et al. 2016; Evofem 2020). In AMP001, bacterial vaginosis was reported as an adverse event in 160 of 1,458 subjects (10.9%) in the Phexxi arm compared to 170 of 1,477 (11.5%) in the Conceptrol arm. Similar rates of BV between the Phexxi and the Conceptrol arm would argue against citrate-containing products such as Phexxi having anti-BV activity.

Reviewer's Comment*: We reviewed the Applicant's submission and the available literature on the effect of citrate-containing products at a similar pH and concentration as DARE-BV1 on pathogens. Though the Simoes et al. publication has limitations including a small study size, Acidform did not appear to adequately treat BV.*

In AMP001, assessment for BV was part of the trial and was evaluated using the Amsel criteria. The control arm used Conceptrol which contains sorbic acid and lactic acid as inactive ingredients. As noted by the Applicant, the data from AMP001 showed no difference in the incidence of BV between the citric acid-containing gel Phexxi versus Conceptrol (11.5% versus 10.9%, respectively). The Investigator's Brochure (version 11) for EVO100 noted that the pH for Phexxi and Conceptrol were (b) (4) and (b) (4), respectively; hence, there was not a drastic difference in pH between the two products. Based on the clinical data from the AMP001 trial mentioned above, the citric acid-containing Phexxi gel did not reduce the incidence of BV as compared to Conceptrol. Hence, we agree with the Applicant that there does not appear to be clinical evidence of efficacy for another citric acid-containing intravaginal drug product with a similar pH and citric acid concentration as in DARE-BV1 for treatment of BV.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Clindamycin phosphate is currently marketed for intravaginal use as a 2% single-dose cream (Clindesse®), 2% cream dosed daily for 3 to 7 days (Cleocin), and 100 mg ovules dosed once daily for 3 days (Cleocin ovules) for the treatment of BV. The amount of clindamycin phosphate (100 mg), administration route, and treatment duration of Xaciato are supported by the safety of

the active pharmaceutical ingredient in these products. The Xaciato product contains three excipients not yet approved for vaginal administration: poloxamer-407, xanthan gum, and sodium citrate dihydrate. No mutagenic or clastogenic effects were detected in vitro or in vivo with poloxamer-407, xanthan gum, or sodium citrate. A mass-balance study in rat with [^{14}C]-poloxamer-407 did not show evidence of widespread distribution of this excipient following vaginal administration.

A 28-day vaginal repeat-dose toxicity study in rabbits conducted with Xaciato did not reveal any excipient-associated safety concerns or potential risks to humans. No evidence of irritation or local toxicity was observed when Xaciato was administered to rabbits at amounts roughly equivalent to the recommended clinical dose based on g/cm^2 vaginal surface area comparisons (see Section III.13). The no observed adverse effect level in this study was 20 mg/day (~6 mg/kg), the only dose tested. The recommended clinical dose of Xaciato is a single administration of 100 mg (~1.6 mg/kg), with an arithmetic mean peak plasma concentration in pre- and post-menopausal women combined of 62 (3.8 to 236) ng/mL, arithmetic mean area under the concentration-time curve (AUC_{0-24h}) of 818 (51 to 3287) h·ng/mL, and plasma half-life of 20 hours. Premenopausal women displayed lower absorption than postmenopausal women, with an arithmetic mean maximum concentration of 11.3 ng/mL and AUC_{0-24h} of 188 h·ng/mL. Toxicokinetics in animals were highly variable following vaginal Xaciato administration (coefficient of variation up to 224%). In rabbits, the mean maximum concentration of 60 ng/mL was approximately equivalent to that in human and the AUC_{0-24h} value of 91.1 h·ng/mL was approximately 0.1-fold that in human at the no observed adverse effect level.

Fertility studies in rats, developmental toxicity studies in rats and rabbits, and pre- and postnatal development studies in rats conducted with vaginally administered Xaciato did not demonstrate evidence of hazard (see Section 8.4).

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Clindamycin is a lincosamide antibacterial drug. Lincosamide antibacterial drugs including clindamycin are associated with *Clostridioides difficile*-associated diarrhea, including cases of severe colitis and death. Another known risk associated with clindamycin is anaphylactic and severe hypersensitivity reactions including toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome. However, because DARE-BV1 is a vaginal gel with low systemic absorption, the risk of *Clostridioides difficile*-associated diarrhea is expected to be low.

Another clindamycin phosphate product administered vaginally is Cleocin vaginal cream (NDA 050680) which is approved in the United States. In clinical trials of Cleocin vaginal cream, the following adverse reactions were observed in ≥1% of participants: vulvovaginal candidiasis, vulvovaginitis, vulvovaginal disorder, trichomonal vaginitis, and pruritus.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Clindamycin phosphate vaginal gel, 2% is not approved in the United States; therefore, no direct postmarketing experience is available. However, clindamycin phosphate vaginal cream, 2%

(Cleocin) is approved in the United States. The Cleocin vaginal cream labeling notes that cases of pseudomembranous colitis have been reported with the use of clindamycin phosphate vaginal cream. Pseudomembranous colitis has historically been used to describe *C. difficile* infection.

7.4. FDA Approach to the Safety Review

The safety review for this NDA was focused on DARE-BV1-001 which was conducted entirely within the United States. Data quality for this study was evaluated using the JumpStart and Core Datafit services. No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. A treatment-emergent adverse event (TEAE) was defined as "any symptom, sign, illness, or experience that developed or worsened in severity and/or frequency after the study drug started"; this definition was acceptable. The Applicant's translations of verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for the events reported in Study DARE-BV1-001 were reviewed and found to be acceptable. Adverse event (AE) terms related to symptoms at the site of drug application, such as vulvovaginal pruritis and vulvovaginal burning sensation, were pooled as vulvovaginal discomfort. The reason for this pooling was that several terms were used to denote these types of symptoms and splitting them up would risk underestimating their incidence. However, there were no major identified issues with respect to recording, coding, and categorizing AEs.

7.5. Adequacy of the Clinical Safety Database

The safety database for DARE-BV1 for the treatment of bacterial vaginosis in adult women is adequate. In FDA's Guidance for Industry, *Bacterial Vaginosis: Developing Drugs for Treatment*, a specific safety database size is not noted. However, because of the available clinical data on clindamycin intravaginal use, the FDA agreed with the Applicant's plan to provide additional safety data from a single well-designed phase 3 trial with a proposed sample size of 200 subjects exposed to DARE-BV1 at the to-be-marketed dose and dosing regimen. The primary safety database for this application is the 202 participants with BV who received a single 5-gram dose of DARE-BV1 in the phase 3 study, DARE-BV1-001. See Table 37 for the baseline demographic and clinical characteristics of the enrolled patient population. There was racial and ethnic diversity in the study population. In addition, the study population was balanced with respect to race and ethnicity.

Of note, study participants were given 25 g of study product with instructions to fill an applicator and administer a single dose of approximately 5 g of gel. Four DARE-BV1 subjects and two placebo subjects reported taking more than one dose of DARE-BV1. In addition, 19 DARE-BV1 subjects and 7 placebo subjects had tube weight differences of the study drug of more than 10.5 g, suggesting that two or more doses were expelled.

An additional 21 healthy female participants received a single 5-gram dose of DARE-BV1 in the pharmacokinetics study, DARE-BV1-PK1. Participants in the pharmacokinetics study did not experience any deaths, serious adverse events (SAEs), or TEAEs that led to discontinuation. The only TEAE was a report of moderate-severity headache. Given the lack of notable safety findings in Study DARE-BV1-PK1, it will not be discussed further in regard to risk and risk management.

7.6. Safety Findings and Concerns Based on Review of the Clinical Safety Database

The demonstrated safety profile of a single 5-gram dose of DARE-BV1 in patients with BV is acceptable. In the single phase 3 trial (DARE-BV1-001), there was a small imbalance with more subjects in the DARE-BV1 arm experiencing at least one TEAE compared to placebo subjects. However, the imbalance was limited to subjects experiencing only mild TEAEs; the incidence of moderate or severe TEAEs was similar between the treatment arms. There was also an imbalance in the incidence of vulvovaginal candidiasis in the DARE-BV1 arm, and most of these cases resolved by the end of the study. Overall, no serious safety concerns were identified in the review of the safety database.

7.6.1. Safety Findings and Concerns, Trial DARE-BV1-001

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary, Trial DARE-BV1-001

Table 18. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Trial DARE-BV1-001

Event	DARE-BV1 N=202 n (%)	Placebo N=103 n (%)
Any TEAE[1]	76 (37.6)	28 (27.2)
Only mild TEAEs	48 (23.8)	15 (14.6)
Moderate or severe TEAEs	28 (13.9)	13 (12.6)
SAEs	0	1 (0.97)
SAEs with fatal outcome	0	0
AEs leading to discontinuation of study drug	0	0
AEs leading to dosage modification of study drug	0	0

Source: Clinical Reviewer.
[1] Includes treatment-emergent AE, defined as any symptom, sign, illness, or experience that developed or worsened in severity and/or frequency after the study drug was administered.
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, Trial DARE-BV1-001

There were no deaths in Trial DARE-BV1-001.

7.6.1.3. Serious Adverse Events, Trial DARE-BV1-001

One subject who received placebo experienced an SAE; no DARE-BV1 subject experienced an SAE.

Subject (b) (6) was a 31-year-old woman who received placebo vaginal gel on (b) (6). On examination at the interim visit on (b) (6), she was noted to have a nodule "post endocervix." On (b) (6), a Pap smear showed "high-grade squamous intraepithelial lesion with features suspicious for invasion." The sample was also noted to be positive for human papillomavirus 16. These findings were recorded as SAEs. The clinical site later reported that the patient underwent surgical removal of the cervix and was found to have squamous cell carcinoma.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial DARE-BV1-001

No study subject experienced a TEAE that led to early discontinuation from the study. Because the study drug was a single dose, there were no early discontinuations of the study drug.

7.6.1.5. Treatment-Emergent Adverse Events, Trial DARE-BV1-001

Table 19 shows the TEAEs occurring in >1% of subjects by treatment arm. Refer to Table 38 for the complete list of TEAEs by system organ class and preferred term.

Table 19. Treatment-Emergent Adverse Events[1] Occurring at ≥1% Frequency in the Treatment Arm Than the Comparator Arm, Phase 3 Safety Population, Trial DARE-BV1-001

Preferred Term[2]	DARE-BV1 N=202 n (%)	Placebo N=103 n (%)
Vulvovaginal candidiasis	35 (17.3)	4 (3.9)
Vulvovaginal discomfort	13 (6.4)	5 (4.9)
Abdominal pain	3 (1.5)	1 (1.0)
Vaginal discharge	3 (1.5)	0 (0)

Source: Clinical Reviewer.
[1] Treatment-emergent adverse event was defined as any symptom, sign, illness, or experience that developed or worsened in severity and/or frequency after the study drug was administered.
[2] Coded as MedDRA preferred terms except the following: vulvovaginal discomfort includes vulvovaginal pruritus, vulvovaginal burning sensation, vulvovaginal erythema, vulvovaginal discomfort, and vulvovaginal dryness; abdominal pain includes abdominal pain and abdominal pain upper.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Medical Officer Comment*: Vulvovaginal candidiasis occurred at a markedly greater frequency among DARE-BV1 subjects compared to placebo subjects; all cases were mild or moderate in severity. Almost all subjects with vulvovaginal candidiasis received treatment for this AE and most cases were resolved or were resolving by the end of the study. Local application of an antibacterial can result in a change in the vaginal microbiome and the risk of candidiasis with vaginal clindamycin has been recognized. The labeling for the listed drug, Cleocin vaginal cream, notes as a precaution that treatment with Cleocin vaginal cream was associated with detection of Candida albicans in 9 to 13% of patients, depending on the study. Vaginal Candida infections will be noted as a warning and precaution (Section 5) and as an adverse reaction (Section 6) in the Xaciato product labeling.*

Vulvovaginal discomfort, which encompasses several preferred terms, occurred in a similar proportion of DARE-BV1 subjects (6%) and placebo subjects (5%).

The incidence of TEAEs among DARE-BV1 subjects did not appreciably differ by race or ethnicity: 44 of 115 (38%) in blacks or African Americans, 31 of 81 (38%) in whites, 17 of 57 (30%) in Hispanics or Latinos, and 58 of 144 (40%) in non-Hispanics or Latinos. The incidence of TEAEs by prior BV history is shown in Table 20.

Table 20. Incidence of Any TEAE by Prior BV History, Safety Population, Trial DARE-BV1-001

Prior BV History	DARE-BV1 n/N (%)	Placebo n/N (%)
No prior BV history	5 of 21 (23.8)	4 of 13 (30.8)
Prior BV history	71 of 181 (39.2)	24 of 90 (26.7)
Three or fewer episodes in last 12 months	50 of 144 (34.7)	16 of 70 (22.9)
Four or more episodes in last 12 months	21 of 37 (56.8)	8 of 20 (40.0)

Source: Clinical Reviewer.
Abbreviations: BV, bacterial vaginosis; N, number of subjects in treatment arm; n, number of subjects with at least one TEAE; TEAE, treatment-emergent adverse event

***Medical Officer Comment**: History of prior BV was common among subjects enrolled in DARE-BV-001 and most subjects had three or fewer episodes in the prior 12 months. TEAEs appeared to be more common among subjects with four or more episodes of BV in the prior 12 months regardless of treatment arm, but the small number of subjects in this category hampers comparison by treatment arm.*

There were 19 DARE-BV1-treated subjects and 7 placebo-treated subjects who had study drug weight differences of 10.5 g or more, suggesting that two or more doses were expelled. The incidence of TEAEs among these subjects was 5 of 19 (26.3%) for DARE-BV1 and 0 of 7 (0%) for placebo. In addition, four DARE-BV1 subjects and two placebo subjects reported using more than one dose of study drug. Among them, one DARE-BV1 subject reported mild vaginal discharge and one placebo subject experienced an AE of mild BV.

***Medical Officer Comment**: The incidence of TEAEs among DARE-BV1 subjects with a tube weight difference of >10.5 g (26%) was similar to that of subjects in the full DARE-BV1 study arm (38%). Given the small number of subjects in the placebo arm with >10.5 g, it is difficult to make any comparisons to the DARE-BV1 arm. These data are reassuring in that administering more than one dose of DARE-BV1 does not appear to be associated with an increased incidence of adverse events. However, there are insufficient data to reach a firm conclusion on the safety of using more than one dose of DARE-BV1.*

(b) (4)

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7.6.1.6. Laboratory Findings, Trial DARE-BV1-001

Review of the laboratory and vital signs data from Trial DARE-BV1-001 did not reveal any meaningful differences between the treatment arms. In addition, there were no potential Hy's Law cases.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Safety in Females 12 to <18 Years of Age

Issue

The review issue is whether there are sufficient safety data in postmenarchal females 12 to <18 years of age to include this population in the indication or whether a postmarket pediatric safety study would be required.

Background

The efficacy of antibacterial drugs in adults is extrapolated to pediatric populations if the pathophysiology of the bacterial infection does not differ significantly from adults to children and the effects of the drug product are sufficiently similar in adult and pediatric populations. However, although some safety information can be gleaned from adult data, the safety in pediatric populations is usually determined from clinical studies in the pediatric populations of interest. During the course of conducting Study DARE-BV1-001, the Applicant revised the protocol to allow enrollment of patients <18 years of age to obtain data in this population. However, the study completed enrollment soon after this protocol change and only one subject <18 years of age was enrolled in the study.

Assessment

The sole subject <18 years of age enrolled in Study DARE-BV1-001 was a 15-year-old female who received DARE-BV1 and experienced no TEAEs.

Because the physiology of postmenarchal females 12 to <18 years of age does not differ drastically from young adult women 18 to 25 years of age, the safety in this young-adult age group was assessed. As noted in Table 21, the incidence of TEAEs in subjects <26 years of age who received DARE-BV1 is similar to that of subjects 26 years and older who received DARE-BV1. The common AEs in the <26-year age group were similar to those in the overall population and included vulvovaginal candidiasis and vulvovaginal pruritis.

Table 21. Incidence of Any TEAE by Age Group, Safety Population, Trial DARE-BV1-001

Age Group	DARE-BV1 n/N (%)	Placebo n/N (%)
Total safety population	76 of 202 (37.6)	28 of 103 (27.2)
<26 years	12 of 36 (33.3)	2 of 17 (11.8)
≥26 years	64 of 166 (38.6)	26 of 86 (30.2)

Source: Clinical Reviewer.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with at least one TEAE; TEAE, treatment-emergent adverse event

Review of the literature did not reveal studies of vaginal clindamycin in the adolescent age group (12 to <18 years of age). However, intravenous and oral clindamycin are approved in this age group for a number of treatment indications, and neither is associated with any age-specific safety issues.

Conclusion

The physiology of postmenarchal females 12 to <18 years of age does not differ drastically from young-adult women and the pathophysiology of BV does not differ by age; the available data on clindamycin do not reveal age-specific safety concerns. Hence, it is reasonable to extrapolate the safety findings from young-adult women to females in the 12 to <18-year age group. The Pediatric Review Committee (PeRC) discussed this application on October 5, 2021 and agreed with the Division's assessment. A postmarket pediatric safety study is not required.

Dissent

Not applicable.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable (local acting drug).

8.2. Drug Interactions

Not applicable (local acting drug).

8.3. Plans for Pediatric Drug Development

See Section 7.7.1 for discussion of the inclusion of female pediatric patients 12 to <18 years of age in the indication. BV does not occur in males and is uncommon in premenarchal females <12 years of age. As a result, no further pediatric drug development is required. In their October 5, 2021 discussion, the PeRC agreed with the Division that efficacy could be extrapolated down to 12 years of age for females and that an additional adolescent study was not needed.

8.4. Pregnancy and Lactation

There are limited data on DARE-BV1 in pregnant women from the phase 3 trial, DARE-BV-001. Subject (b) (6) was 12 weeks pregnant at the time of enrollment. She received DARE-BV1 and was noted to be a clinical cure at the Interim visit but not at the TOC visit. She was reported to have a nonserious "labial lesion" of mild severity. She delivered a healthy neonate via cesarian section and had no complications. In addition, Subject (b) (6) was found to be pregnant at the TOC visit and was thought to have conceived around the time of screening. She received DARE-BV1 and was noted to be a clinical cure at the Interim visit and at the TOC visit. She was reported to have nonserious vaginal burning and itching of moderate severity. She electively terminated the pregnancy at 8 weeks' gestation.

Of note, the listed drug relied upon for this submission, Cleocin Vaginal Cream 2% (NDA 050680) is indicated for the treatment of bacterial vaginosis and can be used to treat non-pregnant and pregnant women during the second and third trimester. Vaginal clindamycin has been widely used for treatment of BV during all trimesters of pregnancy (CDC 2021). Upon discussion with the Division of Pediatric and Maternal Health (DPMH) as well as the Division of Urology, Obstetrics, and Gynecology, and given the low systemic absorption of DARE-BV1, it is concluded that maternal use is not likely to result in significant fetal exposure. Hence, the indication for DARE-BV1 will include the treatment of bacterial vaginosis in female patients 12 years of age and older without specific reference to pregnancy trimesters. Refer to Section III.21 for further discussions.

Prior to submission of the NDA, there were discussions regarding the safety of the benzyl alcohol excipient in the product and its use in pregnancy. DARE-BV1 contains (b) (4) g of benzyl alcohol per dose. The approved drugs Cleocin (clindamycin 2% vaginal cream) and Nuvessa (metronidazole 1.3% vaginal gel) also contain benzyl alcohol at (b) (4) and (b) (4) g, respectively. The labeling for either approved drug does not contain any warning regarding the use of benzyl

alcohol during pregnancy. Given these precedents, the benzyl alcohol level in DARE-BV1 was considered acceptable for use in pregnancy.

Regarding lactation, the transfer of clindamycin into breastmilk is likely to be low as the systemic concentration following intravaginal administration of DARE-BV1 is low. Refer to Section III.21 for additional details. Additionally, refer to the review by DPMH for further discussion on lactation.

The effect of Xaciato on fertility and early embryonic development was evaluated in rats. Treated animals were mated with untreated animals. Females were dosed vaginally with 2 mg daily for 14 days prior to mating, continuing through gestation day (GD) 7. Males were not dosed during the study but exposed during mating. No changes in estrus cycle, cohabitation duration, female mating and fertility indices, number of corpora lutea, implantations, viable embryos, nonviable embryos, pre-implantation loss, postimplantation loss, or in placental examinations were observed during the study. No changes in sperm motility, sperm count, or sperm morphology were observed in males cohabitating with Xaciato-treated females.

Developmental toxicity was evaluated in pregnant rats and rabbits. These animals were given daily vaginal doses of Xaciato at 2 and 20 mg/day, respectively, throughout organogenesis. Rats received drug on GD 6 to 17 and rabbits received drug on GD 7 to 19. No harm to the fetus was observed in either species. The doses tested are approximately equivalent to the applied recommended clinical dose based on g/cm^2 vaginal surface area and body surface area comparisons. Absorption of clindamycin phosphate following vaginal Xaciato administration was relatively low (in ng/mL range) and highly variable. At the doses tested, maximum concentration and $AUC_{0\text{-}24h}$ in pregnant rats and rabbits were roughly equivalent to clinical exposures (see Section III.13).

Pre- and postnatal developmental toxicity were evaluated in rats. Animals were given daily vaginal doses of Xaciato at 2 mg/day during organogenesis and continuing throughout lactation (GD 6 to lactation day 21). No effects on test developmental landmarks or reproductive developmental toxicity were observed for parental and/or first filial generation animals.

The lack of reproductive and developmental hazards associated with clindamycin phosphate administered with the vaginal Xaciato formulation is consistent with findings following oral and parenteral administration noted in the labeling of the LDs. It is noted that the labeling for the LD, Cleocin Vaginal Cream, 2% (NDA 050680), describes observations of cleft palate in fetuses from one mouse strain treated intraperitoneally with clindamycin at 200 mg/kg/day; these data are not included in the labeling for the other LD, Clindamycin in 0.9% Sodium Chloride Injection (NDA 208083). The origin of the intraperitoneal clindamycin study in mice is unknown.

A search of the published literature found a study describing findings in TUC:Sprague-Dawley rats and two strains of mice (TUC:ICR and TUC:CF1) following subcutaneous administration of 100 and 180 mg/kg clindamycin during organogenesis. No effects were observed in Sprague-Dawley rats or CF1 mice. A low incidence of cleft palate was observed in ICR mice, with a litter incidence of 19.2% in the 100 mg/kg group and 11.5% in the 180 mg/kg group compared with 7.4% in controls (Bollert et al. 1974). In a follow-up paper, the same research group examined background rates of cleft palate in ICR mice and found the litter incidence of cleft palate to be 10 to 19% in untreated or vehicle-treated animals (Harris et al. 1980). Although both the LD and the Bollert study describe a cleft palate effect in one strain of mouse, not in

other strains or species, it is unclear if the Bollert study (Bollert et al. 1974) is in fact the study referenced in the labeling.

Based on the available nonclinical studies, the findings of cleft palate in TUC:ICR mice are not recommended for inclusion in Section 8 of the Xaciato labeling given the similar background incidence of cleft palate reported for this strain. The lack of embryo-fetal toxicity observed in rats and rabbits following vaginal Xaciato administration at doses comparable to or exceeding clinical exposures are more relevant and in line with the lack of embryo-fetal toxicity following oral and parenteral administration, as reported in the labeling for the LD, Clindamycin in 0.9% Sodium Chloride Injection (NDA 208083).

9. Product Quality

The NDA, as amended, has provided sufficient chemistry, manufacturing, and controls information to assure the identity, strength, purity, and quality of the proposed drug product, clindamycin phosphate vaginal gel. The proposed drug product is a (b) (4) hydrogel composed of benzyl alcohol, citric acid, poloxamer-407, sodium citrate, xanthan gum, and water, and contains clindamycin (as clindamycin phosphate) at a final concentration of 2%. The recommended dosage of the proposed drug product (clindamycin phosphate vaginal gel) is one applicatorful (5 g of vaginal gel containing 100 mg of clindamycin present as 119 mg of clindamycin phosphate) administered as a single dose intravaginally. The proposed commercial container closure system is a (b) (4) 25 g (b) (4) tube, and the proposed commercial package includes a vaginal applicator to be used for administration of the gel. (b) (4) The overall stability information submitted in the NDA supports 24-month expiration dating for the drug product stored at United States Pharmacopeia controlled room temperature conditions. The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on October 21, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality.

For details refer to the Office of Pharmaceutical Quality Integrated Quality Assessment dated November 14, 2021, and Addendum dated December 2, 2021, in the Document Archiving, Reporting, and Regulatory Tracking System.

9.1. Device or Combination Product Considerations

The drug product commercial packaging presentation includes a (b) (4) disposable vaginal applicator to be used by a patient to administer clindamycin phosphate vaginal gel supplied in a tube. The information submitted in the NDA for the applicator, including on materials, composition, specifications, dose delivery and functionality testing, etc., was evaluated by the Center for Devices and Radiological Health and found acceptable. The Center for Devices and Radiological Health review also includes an assessment of compatibility of the proposed drug product with condoms. The results of condom compatibility studies submitted in the NDA were found acceptable to support the labeling claim indicating compatibility of the gel with natural rubber latex and polyisoprene condoms. However, the labeling should also include a statement that the drug product is not compatible with polyurethane condoms. For details refer to the

Office of Pharmaceutical Quality Integrated Quality Assessment dated November 14, 2021, including the Center for Devices and Radiological Health Consult Review dated November 8, 2021, in the Document Archiving, Reporting, and Regulatory Tracking System.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

There were no issues related to human subject protections or financial disclosures. Routine clinical site inspections were conducted for two investigators: site 125 and site 126. No issues regarding study integrity were found at either clinical site.

11. Advisory Committee Summary

An advisory committee meeting was not held during this marketing application review.

III. Additional Analyses and Information

12. Summary of Regulatory History

Daré Biosciences, Inc. (Applicant) acquired DARE-BV1 (formerly MP101; also referred to as Xaciato in this review) from MilanaPharm in December 2018. On May 3, 2019, the Applicant submitted a request for a Pre-investigational new drug (IND) Written Response Only meeting regarding a proposed development plan for DARE-BV1 in support of a 505(b)(2) marketing application for DARE-BV1 for the treatment of bacterial vaginosis (BV) in nonpregnant adult women. The Division provided a written response on June 27, 2019.

On August 7, 2019, DARE-BV1 (clindamycin phosphate vaginal gel) was granted Qualified Infectious Disease Product designation for the treatment of bacterial vaginosis in women.

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on August 13, 2019. On September 27, 2019, the Applicant requested withdrawal of the iPSP based on the Division's concerns communicated regarding the need for additional nonclinical studies to qualify the excipients in the final product formulation.

On November 15, 2019, the Applicant submitted IND 143919 for DARE-BV1 (clindamycin phosphate vaginal gel) for the treatment of BV in nonpregnant women. The IND contained a phase 3 protocol, DARE-BV1-001, entitled "A Phase 3 Multi-Center, Double-Blind, Placebo-Controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis." There were no clinical hold issues.

The application was granted Fast Track designation for the treatment of BV in women on March 4, 2020.

The Applicant submitted the iPSP on May 22, 2020, and an Agreed iPSP on August 17, 2020. The Division issued an agreement for the iPSP on August 19, 2020. The agreement included a partial waiver request for pediatric females 0 to less than 12 years of age and pediatric males 0 to less than or equal to 17 years of age.

On June 12, 2020, the Applicant proposed the tradename Xaciato. Xaciato was found conditionally acceptable on both September 4, 2020, and August 30, 2021.

On September 18, 2020, the Division agreed that the Applicant's reproductive toxicity studies were adequate to support the enrollment of pregnant women in the phase 3 trial, DARE-BV1-001.

A pre-new drug application (NDA) meeting was requested on November 13, 2020, to discuss the phase 3 study results in support of an NDA for the treatment of BV in adult women. The meeting was held on January 22, 2021. The Office of Pharmaceutical Quality agreed to accept submission of 9-month long-term and 6-month accelerated stability data from three registration batches at the time of NDA submission with an agreement that the 12-month long-term stability data would be provided within 30 days of NDA submission. The Division agreed that a deferral for pediatric

patients aged 12 to less than 17 years might be appropriate because the Applicant reported enrolling only one patient under the age of 18 years. The Applicant reported that DARE-BV1 contains (b) (4)% benzyl alcohol, (b) (4) benzyl alcohol contained in the approved product Cleocin (clindamycin 2% vaginal cream). The Division requested that the Applicant provide additional information regarding the safety of benzyl alcohol as an excipient in drug products intended for use in pregnant women to address whether absorption of benzyl alcohol is the same in the cream and gel formulations. The Division requested that the Applicant submit an amended iPSP outlining the plan for a deferral for females 12 to less than 18 years of age prior to NDA submission.

A Guidance meeting was held on February 8, 2021, to discuss the inclusion of safety information in the proposed product labeling regarding use in pregnancy (b) (4) and to discuss the safety of the benzyl alcohol excipient in the DARE-BV1 formulation in the context of use in pregnant women. The Division communicated that the indicated population will implicitly include pregnant women, but if the Applicant wants pregnant women as a specific indicated population, then a randomized, well-controlled, adequately powered trial in pregnant women with BV would be required. The Division communicated that an indication including the phrase, (b) (4) based on data from the upcoming NDA would not be acceptable. The Applicant informed the Division that (b) (4) and would not be part of the upcoming NDA.

Upon receipt of comments from the Office of Pharmaceutical Quality issued on March 25, 2021, the Applicant cancelled a chemistry, manufacturing, and controls Pre-NDA meeting scheduled for April 1, 2021.

On May 14, 2021, the Applicant submitted a deferral request for an adolescent study of females 12 to less than 18 years of age. An amended agreed iPSP for the deferral was issued on May 27, 2021. (Please also refer to section 8.3 of this review regarding the October 5, 2021 discussion with PeRC and the determination that efficacy could be extrapolated down to 12 years of age for females and that an additional adolescent study was ultimately not needed.)

NDA 215650 for Xaciato (clindamycin phosphate) vaginal gel, indicated for the treatment of BV in adult women was submitted by Daré Biosciences on June 7, 2021. The NDA was filed on August 6, 2021. The NDA is a 505(b)(2) and the review classification is priority.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Clindamycin phosphate is currently marketed for intravaginal use as a 2% single-dose cream (Clindesse®), 2% cream dosed daily for 3 to 7 days (Cleocin), and 100 mg ovules dosed once daily for 3 days (Cleocin ovules) for the treatment of BV. Xaciato contains three excipients not yet approved for vaginal administration: poloxamer-407, xanthan gum, and sodium citrate

dihydrate. Earlier nonclinical studies were conducted to qualify these excipients for vaginal administration, including in vivo and in vitro genotoxicity studies (sodium citrate, poloxamer-407 and xanthan gum), mass balance study (poloxamer-407), and reproductive toxicology studies in rats and rabbits.

Poloxamer-407, xanthan gum, and sodium citrate dihydrate were negative in the Ames and mammalian chromosome aberration assays. In vivo micronucleus assays conducted with poloxamer-407 and sodium citrate dihydrate were also negative (up to 2000 mg/kg, the highest dose tested). An in vivo genotoxicity study with xanthan gum was determined not to be needed based on its presence in another FDA-approved vaginal gel product (Phexxi®). No carcinogenicity studies have been conducted with the excipients. Given the single-dose treatment and negative findings from the genotoxicity test battery, carcinogenicity studies are not indicated.

Following a single vaginal administration of 55 mg/kg [^{14}C]-poloxamer-407, peak plasma levels reached 0.369 µg equivalent/g at 4 hours postadministration, declining steadily thereafter. Plasma levels were below the quantifiable limit 48 hours postadministration and blood concentrations were below the quantifiable limit at all time points postdosing. The distribution of poloxamer-407 was not widespread postdosing; the majority of radioactivity was local within the reproductive system (vagina) and digestive tract. With the exception of bone (femur), all of the tissues had concentrations that were below the quantifiable limit at 168 hours postdosing. Half of the tissues had tissue to plasma ratios of <1.00, and half of the tissues had tissue to plasma area under the concentration-time curve (AUC_{0-t}) ratios of >1.00. The main route of excretion was through feces, with 76.71% of the total [^{14}C]-poloxamer-407-derived radioactivity excreted by 168 hours. No additional radioactivity was recovered from carcass digests. Mean total recovery of 76.71% likely reflects loss of product due to leakage from the administration site once animals were returned to study cages. The radioactivity in the gastrointestinal tract and fecal excretion may be secondary to ingestion of leaked test article (e.g., through grooming, test article transfers onto bedding, etc.) versus poloxamer-407 being directly absorbed in gastrointestinal tissues and subsequently excreted via feces following vaginal administration.

Reproductive toxicology studies were conducted in rats and rabbits with the Xaciato final clinical formulation to evaluate excipient-associated effects on fertility and embryo-fetal development.

A fertility study was performed for female Sprague-Dawley rats using 2 mg/day Xaciato. Females were dosed daily for 2 weeks prior to mating and continued through gestation day (GD) 7; males were not dosed during the study but were exposed during mating. No test-article related changes in estrus cycle, cohabitation duration, female mating and fertility indices, number of corpora lutea, implantations, viable embryos, nonviable embryos, preimplantation loss, postimplantation loss, or placental examinations were observed during the study. No changes in sperm motility, sperm count, or sperm morphology were observed in males cohabitating with Xaciato-treated females.

Developmental toxicity studies in pregnant rats and rabbits revealed no adverse effects on embryofetal development. Sprague-Dawley rats were treated with 0.1 g of Xaciato (2 mg clindamycin phosphate) vaginally once daily from GD 6 to 17, with sacrifice on GD 18. Local administration of Xaciato was approximately 0.1 g/cm^2 based on a vaginal surface area of 1.0 cm^2 in rat ("Anatomy and Physiology" 1957), approximately 1.6-fold local administration of

Xaciato in humans (0.06 g/cm^2 for 5 g dose and reported mean vaginal surface area of 87.46 cm^2) (Pendergrass et al. 2003).

New Zealand White rabbits were treated with 1 g of Xaciato (20 mg clindamycin phosphate) once daily from GD 6 to 19, with sacrifice on GD 29. Local administration of Xaciato was approximately 0.04 g/cm^2 based on a vaginal surface area of ~24.5 cm^2 in rabbit (Oh et al. 2003), approximately 0.7-fold local administration of Xaciato in human.

Absorption of clindamycin phosphate was relatively low (ng/mL range) and highly variable following vaginal Xaciato administration in both rats and rabbits (Table 22 and Table 23).

Table 22. Toxicokinetics of Clindamycin in Pregnant Rats

Dose (mg/day)	Gestation Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (h·ng/mL)
2	6	135	8.0	1850
	17	43.4	8.0	621

Source: Study report 858-0016-DR.
Data are presented as means±SD for C_{max} and AUC_{0-24h} values, and medians (range) for T_{max}.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time to maximum concentration

Table 23. Toxicokinetics of Clindamycin in Pregnant Rabbits

Dose (mg/day)	Gestation Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (h·ng/mL)
20	6	36.5±19.9	1.0 (0.5 to 1.0)	253±340
	19	175	2.3	913

Source: Study report 858-0017-DR.
Data are presented as means±SD for C_{max} and AUC_{0-24h} values, and median (range) for T_{max}.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time to maximum concentration

Clindamycin phosphate exposure after vaginal Xaciato administration in patients is expected to be low. Given the variability in clindamycin phosphate exposures observed in animals, and slight differences in AUC calculations (AUC_{0-24h} in animals versus AUC_{0-inf} in patients), safety margins calculated on an AUC basis are not likely to be informative. The amount of clindamycin phosphate (100 mg), administration route, and treatment duration of Xaciato is supported by the safety of the active pharmaceutical ingredient in the listed drug (LD) Cleocin Vaginal Cream, 2% (NDA 050680). As such, comparisons based on amount of product applied per vaginal surface area can better inform on the lack of adverse developmental outcomes observed when animals were dosed with the final clinical formulation of Xaciato as well as any potential localized toxicity associated with excipient exposure. Overall, safety margins calculated based on exposures (AUC), body surface area (either mg/m^2 or mg/kg), and localized (vaginal) surface area (g/cm^2) are roughly equivalent to clinical exposures Table 24.

Table 24. Xaciato Safety Margins

	Safety Margin			
Species	C_{max}[1]	AUC_{0-24h}[1]	BSA	Vaginal Surface Area
Rat	2.5	1.1	0.6	1.67
Rabbit	0.9	0.8	1	0.7

Source: Nonclinical Reviewer's analysis.
[1] Based on PK data from pre-and postmenopausal women receiving a single dose of Xaciato.
Abbreviations: AUC, area under the concentration-time curve; BSA, body surface area; C_{max}, maximum concentration; PK, pharmacokinetic

Table 25 lists the Xaciato (Clindamycin 2% Vaginal Gel) and excipient toxicology studies that were reviewed under IND 143919.

Table 25. Toxicology Studies Reviewed

Study Number	Study Title	GLP
ADME		
C20073	Mass Balance and Tissue Distribution Using Quantitative Whole Body Autoradiography (QWBA) in Female Sprague-Dawley Rats Following a Single Vaginal Administration of [^{14}C]-poloxamer-407	No
Genotoxicity		
858-0003-GT	Poloxamer-407: Bacterial Reverse Mutation Assay	Yes
858-0005-GT	Xanthan Gum: Bacterial Reverse Mutation Assay	Yes
858-0007-GT	Sodium Citrate Dihydrate: Bacterial Reverse Mutation Assay	Yes
858-0004-GT	Poloxamer-407: In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary Cells	Yes
858-0006-GT	Xanthan Gum: In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary Cells	Yes
858-0008-GT	Sodium Citrate Dihydrate: In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary Cells	Yes
858-0022-GT	Poloxamer-407: Peripheral Blood Micronucleus Assay by Oral Gavage in Rats	Yes
858-0020-GT	Sodium Citrate Dihydrate: Peripheral Blood Micronucleus Assay by Oral Gavage in Rats	Yes
Reproductive Toxicity		
858-0015-DR	Clindamycin 2% Vaginal Gel: Vaginal Dose Study on Fertility and Early Embryonic Development to Implantation in Rats	Yes
858-0016-DR	Clindamycin 2% Vaginal Gel: Vaginal Dose Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rats	Yes
858-0017-DR	Clindamycin 2% Vaginal Gel: Vaginal Dose Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rabbits	Yes

Source: Nonclinical Reviewer.
Abbreviations: ADME, absorption, distr bution, metabolism, excretion; GLP, good laboratory practices

13.2. Individual Reviews of Studies Submitted to the NDAToxicology

13.2.1.1. General Toxicology

Study No. 3015-005/A 28-Day Vaginal Toxicity Study in Rabbits

Key Study Findings

- The no observed adverse effect level in this study was the only dose tested, 20 mg (~5.7 to 6.5 mg/kg), receiving drug daily for 28 days.
- Systemic exposure to clindamycin decreased following daily intravaginal administration, with mean AUC_{Tlast} of 892 h·ng/mL and 160 h·ng/mL on Day 1 and Day 28, respectively. Mean maximum concentrations (C_{max}) on Day 1 and Day 28 were 97.0 and 60 ng/mL, respectively. Variability in mean plasma concentrations was relatively high, with coefficient of variation values ranging from 82.9% to 140% on Day 1 and from 44.1% to 224% on Day 28.

Table 26. Study Information

Study Features and Methods	Details
GLP compliance	Yes: 21 CFR Part 58; OECD
Dose and frequency of dosing	20 mg daily for 28 days (~5.7 to 6.5 mg/kg)
Route of administration	Vaginal
Formulation/vehicle	Xaciato/placebo control HEC
Species/strain	Rabbit/HRA:(NZW)SPF
Number/sex/group	5 Females/group
Age	7.5 months
Satellite groups/unique design	Positive control 4% nonoxynol-9/saline control
Deviation from study protocol affecting interpretation of results	None

Source: Study report 3015-005.
Abbreviations: CFR, Code of Federal Regulations; GLP, good laboratory practices; HEC, hydroxyethyl cellulose; OECD, Organisation for Economic Cooperation and Development

No test article-related changes in body weights, clinical observations, clinical pathology, and macroscopic or microscopic findings of reproductive tissues were observed. The average vaginal irritation index for the placebo control and Xaciato groups were ≤1, indicating no irritation. Both the Xaciato and hydroxyethyl cellulose (HEC) placebo control were comparable to the saline control group.

Table 27. Toxicokinetics of Clindamycin in Female Rabbits

Dose (mg)	Day	Statistic	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/mg)	T_{max}[a] (hr)	T_{last}[a] (hr)	AUC_{Tlast} (hr*ng/mL)	AUC_{Tlast}/Dose (hr*ng/mL/mg)	AUC_{0-24hr} (hr*ng/mL)	AUC_{0-24hr}/Dose (hr*ng/mL/mg)	R^b
20	1	N	5	5	5	5	3	3	1	1	NA
		Mean	97.0	4.85	0.5	2	892	44.6	48.9	2.45	NA
		SD	110	5.49	(0.5-8)	(1-8)	752	37.6	NA	NA	NA
		CV%	113	113	NA	NA	84.3	84.3	NA	NA	NA
20	28	N	5	5	5	5	5	5	3	3	3
		Mean	60.0	3.00	1	4	160	8.01	91.1	4.55	0.403
		SD	65.0	3.25	(0.5-8)	(2-8)	221	11.1	60.0	3.00	0.322
		CV%	108	108	NA	NA	138	138	65.9	65.9	79.9

NA - Not applicable.
SD and CV are not calculated or not reported when N < 3.
a: Median (minimum - maximum), median value only reported if actual collection interval.
b: $R = AUC_{Tlast\ Day\ 28}/AUC_{Tlast\ Day\ 1}$.

Source: Study report 3015-005.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; CV, coefficient of variation; N, number of samples; R, ratio; SD, standard deviation; T_{max}, time to maximum concentration

13.2.1.2. Reproductive Toxicology

Study Number/ Title: 858-0018-DR/ Clindamycin 2%Vaginal Gel: Pre- and Postnatal Development Vaginal Dose Toxicity Study in Rats

Key Study Findings

- The no observed adverse effect level in this study for maternal toxicity and pre- and postnatal developmental toxicity in first filial generation rats was the highest dose tested, 2 mg/day (~5.7 to 6.5 mg/kg), when administered vaginally from implantation GD 6 through weaning (lactation day 21).
- An apparent decrease in systemic exposure for clindamycin was observed at lactation day 21 compared with GD 6: mean C_{max} and AUC_{0-24h} of clindamycin on lactation day 21 were 20.4 ng/mL and 225 h·ng/mL, respectively; mean C_{max} and AUC_{0-24h} of clindamycin on GD 6 were 126 ng/mL and 1160 h·ng/mL, respectively

Table 28. Methods of Vaginal Pre-and Postnatal Developmental Study in Rats

Parameter	Method Details
GLP compliance	Yes: 21 CFR Part 58; OECD
Dose and frequency of dosing	2 mg/day from gestation day (GD) 6 through lactation day 21
Route of administration	Vaginal
Formulation/vehicle	Clindamycin 2% vaginal gel (Xaciato)
Species/strain	Rat (*Rattus norvegicus*/Crl:CD®[Sprague-Dawley] VAF/Plus®/SPF)
Number/sex/group	30 mated females/group
Satellite groups	4 F/control and 8 F/test article for TK
Study design	Mated females were vaginally administered clindamycin 2% vaginal gel (Xaciato) or control (HEC placebo gel) from GD 6 through lactation day 21. Two pups/sex were selected randomly for all available main study litters on PND 22 and divided into cohorts of eight pups/sex/group (one pup/sex/litter) for evaluations of developmental landmarks including, but not limited to, functional observational battery (PND 43 to 49), learning and memory test (PND 64 to 84), and reproductive development (PND 77 to 90).
Deviation from study protocol affecting interpretation of results	None

Source: Study report 858-0018-DR.
Abbreviations: CFR, Code of Federal Regulations; F, female; GD, gestation day; GLP, good laboratory practice; HEC, hydroxyethyl cellulose; OECD, Organisation for Economic Cooperation and Development; PND, postnatal day; SPF, specific-pathogen free; TK, toxicokinetics

Table 29. Observations and Results

Parameter	Major Findings
Mortality	None
Clinical signs	None
Body weights	None
Necropsy findings	None
Cesarean section data	None
Necropsy findings	None
Offspring	None

Source: Nonclinical Reviewer's analysis.

No test article-related changes on mortality, clinical observations, gestation duration, development landmarks, reflex and sensory development, automated motor activity test, functional observational battery test, accelerating rotarod test, learning and memory test, and reproductive developmental toxicity were observed for parental and/or first filial generation animals in the study.

Table 30. Toxicokinetics of Clindamycin in Pregnant and Lactating Female Rats

Dose (mg/day)	Study Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (h·ng/mL)
	GD 6	126	2.0	1160
2	LD 4	100	2.0	564
	LD 21	20.4	4.0	225

Source: Study report 858-0018-DR.
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum concentration; GD, gestation day; LD, lactation day; T_{max}, time to maximum concentration

13.2.2. Impurities/Degradants

There are no impurities, degradants, or extractables/leachables associated with Xaciato that are likely to pose a safety concern from a Pharmacology/Toxicology perspective. Specification limits for lincomycin-2-phosphate (not more than 1.0%) and clindamycin b-2-phosphate (not more than 1.5%) appear below the clindamycin phosphate United States Pharmacopoeia monograph and testing of the drug product housed in the aluminum tube container closure system did not identify any leachables of concern. No leachables study was conducted on the drug product in the (b) (4) applicator. However, given its use in other approved vaginal products and lack of cytotoxicity, vaginal irritation, or hypersensitivity findings associated with test article extracts, the applicator is unlikely to pose a safety concern when used to administer Xaciato.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

The Applicant proposed to rely on the reference listed drug, Clindamycin Phosphate Intravenous Solution (NDA 208083; Baxter Healthcare Corporation, approved on April 20, 2017), for safety based on lower systemic clindamycin exposure (C_{max} and AUC) after administration of DARE-BV1 compared to the one following intravenous (IV) infusion of clindamycin phosphate at the highest approved strength (900 mg), as described in the approved labeling of the LD. The systemic exposure of DARE-BV1 was measured in Study DARE-BV1-PK1.

Pharmacokinetic Study of DARE-BV1 (Study DARE-BV1-PK1)

The clinical pharmacokinetic (PK) study of DARE-BV1 (DARE-BV1-PK1) was designed as a single-center, phase 1, single-dose, open-label PK study in healthy female subjects. One full

applicator (5 g gel, 100 mg clindamycin phosphate) of DARE-BV1 was administered to the subjects intravaginally on Day 1. Plasma PK samples and vaginal PK samples from 21 healthy female subjects were collected daily through Day 7 after treatment with DARE-BV1. A fully validated liquid chromatography with tandem mass spectrometry method was used for the quantification of plasma clindamycin concentration. The liquid chromatography with tandem mass spectrometry method used to determine plasma clindamycin concentration is acceptable. However, the validation of the bioanalysis method used to determine vaginal clindamycin concentration is inadequate, and so an Information Request letter was sent to the Applicant on August 18, 2021. The Applicant responded on August 25, 2021, that "*vaginal clindamycin phosphate concentrations were not used nor intended to support any claims of safety or efficacy, nor to be used in any label statements*."

The PK parameters obtained following a single intravaginal dose of 100 mg of DARE-BV1 administered to 21 healthy female subjects are summarized in Table 31.

Reviewer's Comment: *Based on the labeling of Clindamycin Phosphate in 0.9% Sodium Chloride Injection (NDA 208083), the average serum elimination half-life of clindamycin is about 3 hours in adults and 2.5 hours in pediatric patients, which are both much shorter than the clindamycin half-life observed in DARE-BV1. Based on the vaginal PK data in Study DARE-BV1-PK, the half-life of clindamycin in the vaginal area estimated by the reviewer is around 25.98 hours. Therefore, the observed clindamycin systemic half-life in DARE-BV1, 20 hours, might be caused by the slow vaginal absorption.*

Of note, only 9 of 21 subjects were included in the $AUC_{0-\infty}$ calculation and only 10 of 21 subjects were included in the half-life calculation.

Table 31. Summary of Plasma Clindamycin Pharmacokinetic Parameters

Parameter Statistic	Overall N=21
C_{max} (ng/mL)	
N	21
Mean	69.2
GM	31.4
CV (%)	113
AUC_{0-t} (h·ng/mL)	
N	21
Mean	1179
GM	754
CV (%)	85.1
$AUC_{0-\infty}$ (h·ng/mL)	
N	9
Mean	1975
GM	1610
CV (%)	53.2
AUC_{0-24} (h·ng/mL)	
N	21
Mean	818
GM	415
CV (%)	112
T_{max} (h)	
N	21
Median	6.00
(minimum, maximum)	(4.00, 95.83)
$t_{1/2}$ (h)	
N	10
Mean	20.0
GM	11.8
CV (%)	151
T_{last} (h)	
N	21
Median	48.4
(minimum, maximum)	(24.00, 145.15)
C_{last} (ng/mL)	
N	21
Mean	3.54
GM	2.27
CV (%)	104

Source: Study report DARE-BV1-PK1.
Note: The $t_{1/2}$ for subjects with adjusted R^2<0.8 was not summarized. The AUC_{inf} for subjects with the adjusted R^2<0.8 or $AUC_{\%extrap}$ >20% were not summarized. $AUC_{0-\infty}$ and $t_{1/2}$ could not be determined for several subjects due to less than 3 points in the elimination phase.
Abbreviations: $AUC_{\%extrap}$, area under the concentration-time curve extrapolated as a percentage of the total; AUC_{0-x}, area under the concentration-time curve from time 0 to the time indicated; C_{last}, last measurable concentration; C_{max}, maximum concentration; CV, coefficient of variation; GM, geometric mean; n, number of subjects in the respective category; R^2, square of the correlation coefficient; SD, standard deviation; $t_{1/2}$, elimination half-life; T_{last}, time to last measurable concentration; T_{max}, time to maximum concentration

PK Properties of Clindamycin Phosphate in 0.9% Sodium Chloride IV Injection

Based on the most recent LD labeling of Clindamycin Phosphate in 0.9% Sodium Chloride IV Injection (NDA 208083) (Baxter 2021), the highest recommended daily dose is 900 mg

clindamycin, every 8 hours. The peak serum concentration of clindamycin following IV infusion of 900 mg is 14.1 µg/mL (Table 32). The AUC information is not in the LD's label. Therefore, the C_{max} of clindamycin after the proposed dose of DARE-BV1 intravaginally is around 0.5% compared to the C_{max} after an IV infusion of 900 mg clindamycin, every 8 hours (Table 33). The review team agreed with the Applicant that the systemic exposure of clindamycin after administration of a single dose (100 mg) of DARE-BV1 is significantly lower compared to the systemic exposure (C_{max}) following IV infusion of clindamycin phosphate at the highest approved dose.

Table 32. Average Peak and Trough Serum Concentrations of Active Clindamycin After Dosing From LD's Label

Dose	Peak (µg/mL)	Trough (µg/mL)
Healthy adult males (post equilibrium)		
600 mg IV in 30 minutes q6h	10.9	2.0
600 mg IV in 30 minutes q8h	10.8	1.1
900 mg IV in 30 minutes q8h	14.1	1.7
Pediatric patients (first dose)[1]		
5 to 7 mg/kg IV in 1 hour	10	

Source: Label of Clindamycin Phosphate in 0.9% Sodium Chloride IV Injection (NDA 208083) (dated February 18, 2021).
[1] Data in the group of patients being treated for infection.
Abbreviations: IV, intravenous; LD, listed drug; q6h, every 6 hours; q8h, every 8 hours

Table 33. Mean Clindamycin Pharmacokinetic Parameter Comparison Between Intravaginally Administered DARE-BV1 and IV Infusion of Clindamycin Phosphate

Parameter	Intravaginal DARE-BV1 (100 mg)	IV Clindamycin Phosphate (900 mg q8h)
C_{max} (µg/mL)	0.07	14.10[1]
AUC_{0-t} (µg·h/mL)	1.18	Not available
$AUC_{0-\infty}$ (µg·h/mL)	1.97[2]	Not available

Source: Label of Clindamycin Phosphate in 0.9% Sodium Chloride IV Injection (NDA 208083) (dated February 18, 2021) and study report DARE-BV1-PK1.
[1] Based on the labeling, it is unknown whether the C_{max} was obtained following a single dose IV infusion of clindamycin phosphate or the one at steady state after multiple doses, but it would not affect the conclusion that the C_{max} following intravaginal administration of DARE-BV1 is markedly lower compared to that after IV infusion.
[2] N=9; Subjects with adjusted R^2 <0.8 and subjects with $AUC_{\%extrap}$ >20% were excluded.
Abbreviations: $AUC_{\%extrap}$, area under the concentration-time curve extrapolated as a percentage of the total; AUC_{0-x}, area under the concentration-time curve from time 0 to the time indicated; C_{max}, maximum concentration; IV, intravenous; q8h, every 8 hours

Plasma Clindamycin Levels During Menopause and Premenopause

The Applicant also compared the systemic exposure between women during menopause and premenopause, because the vaginal atrophy resulting from menopause can allow greater absorption of intravaginally applied drugs. The study results showed expected results that the premenopausal women had lower systemic exposure with an arithmetic mean C_{max} of 11.3 ng/mL and AUC_{0-24h} of 188 h·ng/mL, compared with 92.3 ng/mL and 1070 ng·h/mL, respectively, among postmenopausal women.

Reviewer's Comment*: The systemic exposure in postmenopausal women after administration of the proposed dose of DARE-BV1 is markedly lower compared to that after a single dose of 900 mg clindamycin phosphate IV infusion.*

Vaginal Clindamycin Concentrations

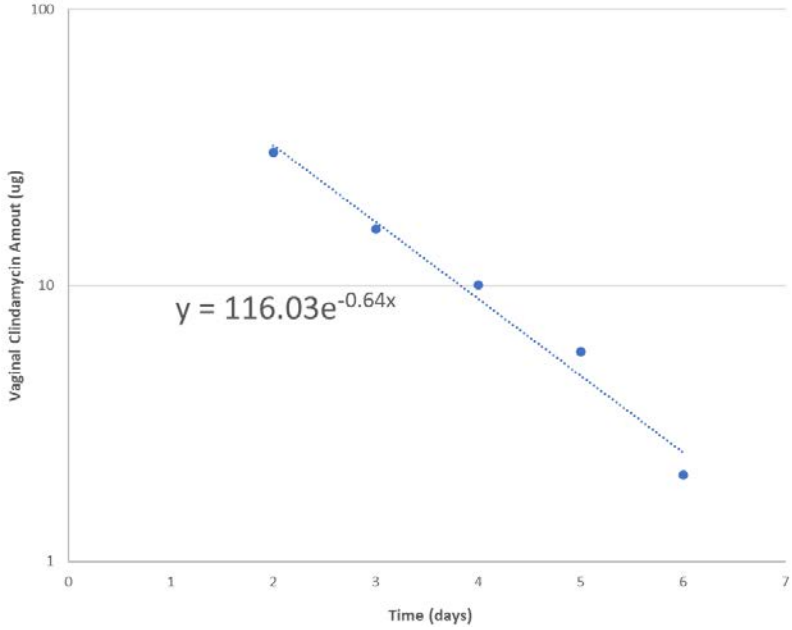
Clindamycin phosphate levels, as measured from vaginal swabs were relatively high after 24 hours following administration of DARE-BV1 in 15 of the 21 subjects (i.e., 6 subjects had

values greater than 400 µg/g, and 9 had values between 100 and 400 µg/g). The levels dropped off in most participants to below the limit of quantitation 2 days following dosing. In four participants, levels remained elevated for several days. The mean amount decreased by approximately 50% on Day 3.

The reviewer plotted mean vaginal clindamycin amount as a function of time (Figure 1), which suggests that the elimination of clindamycin from the vagina followed first-order linear regression with a half-life of around 1.08 days (25.99 hours).

Of note, vaginal clindamycin phosphate concentrations were not used or intended to support any claims of safety or efficacy, or to be used in any labeling statements.

Figure 1. Mean Vaginal Clindamycin Amount Over Time



Source: Clinical Pharmacology Reviewer-generated figure, based on the data submitted in study report DARE-BV1-PK1.

14.3 Summary of Bioanalytical Method Validation and Performance

The Clinical Pharmacology team reviewed the bioanalytical method validation and sample analysis reports for the quantification of clindamycin in human plasma and found the analyses to be acceptable. Validation results for the bioanalytical methods are summarized in Table 34.

Table 34. Bioanalytical Method for Quantitation of Clindamycin in Human Plasma

Method Parameter	Method Information
Bioanalytical method validation report location	4086 Assay Validation Report
Analyte	Clindamycin
Internal standard	Clindamycin-^{13}C, D3
Method description	Protein precipitation extraction
Limit of quantitation	0.5 ng/mL
Recovery of drug at each QC (%CV)	Avg.: 58.0% (3.8) HQC: 58.6% MQC: 55.5% LQC: 59.8%
Average recovery of IS (%)	Not applicable
Standard curve concentrations (ng/mL)	0.500 ng/mL to 500 ng/mL
QC concentrations (ng/mL)	LLOQQC: 0.500 LOQQC: 1.500 MLOQQC: 15.0 MQC: 150 HQC: 375
QC intraday precision range (%)	LLOQQC: 9.62 to 13.4 LQC: 5.92 to 6.94 MLOQ: 3.32 to 7.35 MQC: 2.18 to 4.82 HQC: 5.08 to 6.15
QC intraday accuracy range (%)	LLOQQC: 95.2 to 99.2 LQC: 105.65 to 106.94 MLQC: 103.32 to 107.35 MQC: 102.18 to 104.82 HQC: 105.08 to 106.15
QC interday precision (%)	LLOQQC: 10.56 LQC: 7.01 MLQC: 5.14 MQC: 3.86 HQC: 5.66
QC interday accuracy (%)	LLOQQC: 96.4 LQC: 102.7 MLQC: 102.7 MQC: 101.3 HQC: 103.7
Bench-top stability (h)	6 hours at ambient temperature
Stock stability (days)	106 days at -20°C
Processed stability (h)	21 hours at ambient temperature 148 hours at 2 to 4°C
Freeze-thaw stability (cycles)	9 cycles
Long-term storage stability (days)	3 days at -20°C 58 days at -80°C
Dilution integrity	1500 ng/mL diluted ten-fold 6% from nominal, CV=5.2%
Selectivity	No interfering peaks noted in blank plasma samples

Source: Study report 4086 by (b) (4)
Abbreviations: CV, coefficient of variation; HQC, high quality control; IS, internal standard; LQC, low quality control; LLOQQC, lower limit of quantitation quality control; LOQQC, limit of quantitation quality control; MLOQ, mid limit of quantitation; MLQC, mid-low quality control; MMLOQQC, middle limit of quantitation quality control; MQC, middle quality control

Table 35. Key Bioanalysis Review Questions

Parameter	Result
Is the same anticoagulant used in the pre-method validation study and pharmacokinetics sample analysis?	☒ Yes (K_2EDTA) ☐ No
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes[1] ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Source: Study report 4086 by (b) (4).
[1] In the IR response dated August 25, 2021, the Applicant updated the long-term stability information which has been collected at -80°C for 90 days, which covers the storage period of 88 days at -80°C.
Abbreviations: IR, Information Request; LTSS, long-term storage stability; QC, quality control

Table 36. Key Bioanalysis Review Questions

Parameter	Result
Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Plasma samples concentration range: 0.538-729.87 ng/mL
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)?	☐ Yes ☒ No
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No

Source: Study report 4086 by (b) (4).
Abbreviation: QC, quality control

However, after a review of the bioanalytical validation report for vaginal samples, based on the FDA *Bioanalytical Method Validation* Guidance,[2] the following was found:

- The provided accuracy results for middle quality control and low quality control did not meet the acceptance criteria (within ±15% of nominal concentrations).
- The accuracy and precision results for low quality control were not provided.
- Both intraday and interday accuracy and precision are required to be evaluated; however, the Applicant only provided one accuracy and one precision result without specifying whether they were for interday or intraday.
- Several stability related evaluation data were missing including stock stability, process stability, bench-top stability, freeze thaw stability, and long-term stability.

Therefore, the vaginal clindamycin concentration data in the phase 1 study DARE-BV1-PK1 may not be used to support the efficacy of the proposed drug product, DARE-BV1 (clindamycin phosphate) Vaginal Gel 2%, for the treatment of bacterial vaginosis in adult women. In the Information Request response dated August 15, 2021, the Applicant stated that vaginal clindamycin phosphate concentrations were not used or intended to support any claims of safety or efficacy, or to be used in any labeling statements.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

15. Trial Design: Additional Information and Assessment

The following is the DARE-BV1-001 protocol synopsis copied from protocol version number 4.0, dated August 14, 2020.

Title of Study

A Phase 3 Multi-center, Double-Blind, Placebo-controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis

Study Centers

Approximately 36 sites in the United States.

Study Period

The study duration for each patient was up to approximately 1 month:

- Visit 1 (Day 1) screening and randomization, including treatment;
- Visit 2 (Day 7 to 14) interim assessment of efficacy parameters and safety; and
- Visit 3 (Day 21 to 30) assessment of clinical cure and safety or the Follow-up Safety Phone Visit (Day 21 to 30) for patients who discontinue prematurely from the study.

For patients in the PK subset only, there were additional blood draws at Visit 1 (Day 1) as well as five additional visits between Visit 1 and Visit 2 (Visits PK1 to PK5 on Days 2 to 6).

Objectives

Primary

Assess the efficacy of DARE-BV1 for the treatment of BV in postmenarchal females.

Secondary

Assess the safety and acceptability of DARE-BV1.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study of DARE-BV1 (clindamycin phosphate vaginal gel, 2%) (once daily [QD] × 1 day) compared to placebo vaginal gel (HEC Universal Placebo Gel) (QD × 1 day) for the treatment of BV. Patients were evaluated at three time points: a Day 1 Screening/Randomization visit, a Day 7 to 14 Interim Assessment visit, and a Day 21 to 30 test-of-cure [TOC] visit). Patients who discontinued prematurely from the study received a safety follow-up telephone call between Day 21 to 30. The total study duration was up to approximately 1 month for each patient.

The date of the patient's last menstrual period and expected timing of her next menses will need to be taken into consideration prior to scheduling the Screening/Randomization visit to ensure the patient is not menstruating at the time of the visit, nor expected to start menstruating during

the first 7 days after study drug administration. In the event that the patient is found to be menstruating at the time of the initial Screening/Randomization visit, or is due to start menstruating within 1 week of the visit, then randomization should be delayed. Split screening visits are therefore allowed (while noting protocol requirements for those assessments that must be repeated or delayed until the day of randomization).

At the Screening/Randomization visit (Day 1), past medical and obstetrical/gynecological history, contraception and medically relevant sexual history, and number of episodes of BV in the preceding 12 months (along with treatment given) were collected/evaluated. Signs and symptoms of BV were evaluated, including color, odor, and consistency of vaginal discharge, plus vulvovaginal itching and irritation were assessed. Additionally, the following samples/tests were collected and performed: saline wet mount to assess clue cell percentage, 10% potassium hydroxide (KOH) whiff test, and KOH wet mount microscopy for yeast assessment, vaginal culture for *Candida* species, vaginal pH, preparation of slides for centralized Gram stain for Nugent scoring, urine pregnancy test, nucleic acid amplification tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, OSOM® test for *Trichomonas vaginalis*, blood sample for chemistry and hematology, and urinalysis.

Patients were provided with instructions for using a daily electronic diary. The patient electronic diary was used to collect information regarding study drug administration, symptoms related to BV, relevant adverse events (AEs), and other pertinent factors.

Eligible patients were randomly assigned via Interactive Response Technology to one of the following treatment groups (2:1): clindamycin phosphate vaginal gel, 2% (DARE-BV1; 1 dose is 5 g gel=100 mg clindamycin) QD × 1 day, or placebo vaginal gel (Universal HEC Placebo Gel, 5 g), QD × 1 day. Study drug was applied intravaginally within 1 day of randomization.

The patients returned to the clinic for Visit 2 on Day 7 to 14 for the Interim Assessment. A third and final visit was conducted at Day 21 to 30 for TOC. Similar to the requirement at randomization, patients should not have been actively menstruating on the day of the Interim or TOC visit, although the TOC visit should take priority if scheduling around menses is challenging. At both Visit 2 (Day 7 to 14) and Visit 3 (Day 21 to 30), the Investigator performed gynecological examinations and collected specimens for the following tests: saline wet mount to assess clue cell percentage, 10% KOH whiff test and wet mount microscopy for yeast assessment, vaginal pH, preparation of slides for centralized Gram stain for Nugent scoring, urinalysis, and urine pregnancy test. Additionally, the signs and symptoms of BV—including color, odor, and consistency of vaginal discharge, plus vulvovaginal itching and irritation—were evaluated at each visit. Post-treatment blood chemistry and hematology assessments were conducted at the TOC visit (Visit 3, Day 21 to 30). Repeat testing for *N. gonorrhea*, *C. trachomatis*, *T. vaginalis*, or *Candida* species could be performed at any time if clinically warranted to determine the etiology of a change or worsening in vaginal discharge or other signs or symptoms.

Assessment and documentation of AEs and concomitant medications occurred at each visit. A review of patient-reported and Investigator-assessed local site reactions also took place at each visit after randomization and treatment.

Approximately 20 patients at selected sites participated in a PK study. The patients in this subset applied the study drug during Visit 1 at the study clinic and underwent blood draws for plasma clindamycin assessment at 0 hours (predose) and then at 2, 4, 6, and 8 hours (±15 minutes)

postdose, as well as at 24, 48, 72, 96, 120, and 144 hours (±2 hours) postdose (Days 2 to 7). In addition, samples for vaginal clindamycin concentrations were collected on Days 1 to 7 (with the Day 1 sampling schedule starting predose). For these patients, the assessments for the Interim Assessment (Day 7 to 14) visit could be performed on the same day as the Day 7 PK sample collection.

If necessary due to persistent symptoms of BV, patients may be offered other BV treatment prior to completion of the study; however, whenever feasible, other therapy should not be initiated until the patient has completed the final TOC visit (Visit 3, Day 21 to 30). If initiated prior to Visit 3, then the patient should remain in the study and return to the clinic for the final TOC visit (Visit 3, Day 21 to 30). If other BV treatment is prescribed at Visit 3, then the patient should either be followed by the study physician (if the patient is regularly treated at their clinic), or referred back to their local healthcare provider for further follow-up, as appropriate. The choice of other BV therapy is left up to the investigator in collaboration with the patient, based on the current standard of care. Any other medications received for treatment of BV should be recorded as concomitant medications.

The goal was for all patients to complete the study, irrespective of whether additional BV treatment, yeast treatment, or other antimicrobial therapy is required prior to completion of the final TOC visit (Visit 3, Day 21 to 30). Patients who discontinued prematurely from the study for any reason received a safety follow-up telephone call from Study Day 21 to 30 to assess BV symptoms, AEs, and medication usage.

Primary Efficacy Endpoint

- Proportion of patients with clinical cure at the TOC visit (Day 21 to 30). Clinical cure was defined as:
  - Resolution of abnormal vaginal discharge associated with BV;
  - Negative 10% KOH whiff test; and
  - Clue cells <20% of the total epithelial cells in a saline wet mount.

Secondary Efficacy Endpoints

- Proportion of patients with bacteriological cure at the TOC visit (Day 21 to 30). Bacteriological cure was defined as a Nugent score <4.
- Proportion of patients with therapeutic cure at the TOC visit (Day 21 to 30). Therapeutic cure was defined as both a clinical cure (defined above) and bacteriological cure (Nugent score <4).
- Proportion of patients with clinical cure (defined above) at the Interim Assessment visit (Day 7 to 14).
- Proportion of patients with bacteriological cure (Nugent score <4) at the Interim Assessment visit (Day 7 to 14).
- Proportion of patients with therapeutic cure at the Interim Assessment visit (Day 7 to 14).

Safety and Acceptability Assessments

- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- OSOM® test for *Trichomonas vaginalis*
- Nucleic acid amplification tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
- Clinical and microscopic assessment for vulvovaginal candidiasis
- Vaginal culture for *Candida* species
- Review of treatment-emergent adverse events and local site reactions
- Review of concomitant medications
- Acceptability questionnaire

Additional Pharmacokinetic Assessments (PK Subset Only)

- Pharmacokinetic blood draws to assess plasma clindamycin levels for Days 1 to 7
- Vaginal clindamycin concentration levels for Days 1 to 7

Number of Patients (Planned)

Approximately 282 patients were planned to be enrolled.

Diagnosis and Main Eligibility Criteria

Patients with a clinical diagnosis of BV at the Screening/Randomization visit who met the eligibility criteria listed below were eligible to participate in the study.

Inclusion Criteria

(1) Patients must provide written informed consent prior to any study-related procedures being performed. Patients 12 to 17 years old may participate where permitted by applicable local regulations and Institutional Review Board approval and with appropriate documentation of consent from the parent(s)/guardian(s) and assent from the patient.

(2) Patients must have a clinical diagnosis of BV, defined as having all of the following:

  (a) Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina.
  (b) The presence of clue cells >20% of the total epithelial cells on microscopic examination of a saline wet mount.
  (c) Vaginal secretion pH of >4.5.
  (d) A fishy odor of the vaginal discharge upon addition of a drop of 10% KOH (i.e., a positive whiff test).

(3) Patients must be females ≥12 years of age with no known medical conditions that, in the Investigator's opinion, may interfere with study participation.

(4) Patients must agree to abstain from sexual intercourse and/or sexual activity for the first 7 days following treatment. Nonpregnant patients must also agree to use

adequate birth control (see Inclusion Criterion #5) should they later engage in heterosexual intercourse through the final study visit (Visit 3, Day 21 to 30).

(5) This trial will enroll pregnant women; however, nonpregnant patients of childbearing potential should use adequate birth control after Day 7 if engaging in heterosexual intercourse and should not plan on becoming pregnant for the duration of the study. Acceptable forms of birth control include oral contraceptives ("the pill"), intrauterine devices, contraceptive implants under the skin, patches or injections, and nonpolyurethane condoms (e.g., latex, polyisoprene) with or without spermicide. Patients in same-sex relationships, or monogamous relationships with vasectomized males, may also participate. Abstinence may also be acceptable, per the Investigator's judgment. Oral or transdermal hormonal contraceptives must be in use for one full cycle (e.g., 4 to 8 weeks) prior to study drug application. Injectable or implanted contraceptives (e.g., Depo-Provera, Nexplanon, or hormonal intrauterine device) must have been injected/inserted at least 7 days prior to study drug application.

(6) Patients who are not of childbearing potential did not need a urine pregnancy test prior to randomization or at subsequent visits. The patient was considered to be of nonchildbearing potential if one of the following was satisfied:

(a) Postmenopausal for at least 1 year prior to the Screening/Randomization visit (Visit 1) (defined as amenorrheic for more than 1 continuous year), or
(b) Surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) at least 6 months before first dose, or
(c) Nonsurgical permanent sterilization procedure performed at least 3 months prior to study drug application.

(7) Patients must be willing to refrain from the use of all intravaginal products (e.g., douches, feminine deodorant sprays, condoms, spermicides, vaginal moisturizers or lubricants, tampons, vaginal birth control rings [e.g., NuvaRing®], and diaphragms) through at least the first 7 days, and ideally through Visit 3 (Day 21 to 30) or study exit/early discontinuation.

Exclusion Criteria

(1) Patients with active vulvovaginitis or other active infectious causes of cervicitis, vaginitis, or vulvitis, based on the results of the thorough clinical assessments and in-clinic microscopic assessments performed prior to enrollment (e.g., candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or genital lesions or ulcers consistent with human papillomavirus, Herpes simplex, syphilis, chancroid, etc.). Patients with a history of genital herpes or condylomata who have been asymptomatic for at least 6 months may be considered for eligibility.

(2) Potential patients who are breastfeeding or, if of child-bearing potential, unwilling to practice acceptable means of birth control or abstinence during the study as described above.

(3) Patients with a vaginal, vulvar, or genitourinary condition that, according to the Investigator's judgment, may confound the interpretation of clinical response.

(4) Patients with a history of regional enteritis, ulcerative colitis, or a history of *Clostridioides difficile*-associated diarrhea.

(5) Patients with known current drug or alcohol abuse that could impact study compliance.

(6) Patients currently receiving or who have received antifungal or antibacterial therapy (systemic or intravaginal) within 14 days of the Screening/Randomization visit (Visit 1).

(7) Patients who have used any other investigational product within 30 days of the Screening/Randomization visit (Visit 1).

(8) Patients who 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.

(9) Patients with known sensitivity to clindamycin phosphate or other lincosamides or any of the inactive ingredients in the study drug.

(10) Patients with a history of any severe acute or chronic medical or psychiatric condition or laboratory abnormality that could increase the risk associated with trial participation or study treatment administration or could interfere with the interpretation of trial results and, in the judgment of the Investigator, would make the patient inappropriate for entry into the trial.

Test Product, Dose, and Mode of Administration

DARE-BV1 (clindamycin phosphate vaginal gel, 2%) was supplied in tubes with accompanying applicators. To dispense the product, the patient screwed the applicator onto the tube and express product from the tube into the applicator, up to the stop line on the applicator. One full applicator (5 g) of clindamycin phosphate vaginal gel, 2% (100 mg clindamycin) was to be applied intravaginally as a single dose.

Reference Therapy, Dose, and Mode of Administration

Placebo vaginal gel (HEC Universal Placebo Gel) was supplied in matching tubes with accompanying applicators, as above. One full applicator of placebo vaginal gel (5 g) was to be applied intravaginally as a single dose.

Statistical Analyses

All statistical processing was performed using SAS®, version 9.4 or later. Continuous variables were summarized as number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized as frequency counts and percentages.

All efficacy analyses were conducted using a two-sided test at an alpha level of 0.05. The primary efficacy analyses were conducted on the modified intent-to-treat (mITT) population. Additionally, efficacy analyses were performed on the per protocol (PP) population and are considered supportive. Safety analyses were performed on the Safety population. Patients were analyzed according to the treatment to which they were randomized for the intent-to-treat (ITT)

and mITT analyses, regardless of actual treatment received. For all other analysis populations, patients were analyzed according to the treatment received.

Populations

Intent-to-treat (ITT): All randomized patients.

Safety: All ITT population patients who applied study drug.

Pharmacokinetic subset: All Safety population patients enrolled in the PK subset.

Modified intent-to-treat (mITT): All Safety population patients except those excluded for a positive test result for other concomitant vaginal or cervical infections at baseline (e.g., *T. vaginalis, N. gonorrhoeae, C. trachomatis, Candida* species) or who had a baseline Nugent score of <7. If the Nugent score at baseline was missing, the patient was excluded from the mITT population.

Per Protocol (PP): The PP population included patients from the mITT population who received other BV therapy during the study for any reason [and were therefore considered a treatment failure], or met the following criteria:

(1) Met all four Amsel's criteria at screening.
(2) Applied study drug within 1 day of randomization.
(3) Did not use a prohibited medication prior to the Day 21 to 30 visit.
(4) Attended the Day 21 to 30 visit.
(5) Had no other major protocol violations that impacted the primary or secondary endpoints.

For the mITT and PP populations, if the patient received other BV therapy for any reason, the patient was included in the analysis as a treatment failure for all visits on or after receipt of the other therapy. Patients were to be excluded from the PP population if they received study treatment that was not the treatment to which they were randomized. A review of the data was to be performed prior to locking the database and unblinding the study to determine which medications and major protocol violations would impact the primary and secondary endpoints and cause a patient to be excluded from the PP population.

Efficacy Analyses

Efficacy endpoints were to be summarized for each treatment group using descriptive statistics, including 95% confidence intervals (within treatment group), as appropriate.

Primary Efficacy Analyses

The primary efficacy analysis of Clinical Cure at Day 21 to 30 was to be performed for the mITT population by Cochran-Mantel-Haenszel test stratified by study center and race (African American/black versus all others). The method for handling patients in the mITT analysis without a Clinical Cure result at Day 21 to 30 is described in the final Statistical Analysis Plan.

Secondary Efficacy Analyses

Hypothesis testing for the secondary efficacy endpoints was to be conducted in a sequential manner to control the Type 1 error rate, in the order presented below:

- Proportion of patients in the mITT population with bacteriological cure at the TOC visit (Day 21 to 30).
- Proportion of mITT patients with therapeutic cure at the TOC visit (Day 21 to 30).
- Proportion of mITT patients with clinical cure (defined above) at the Interim Assessment visit (Day 7 to 14).
- Proportion of mITT patients with bacteriological cure (Nugent score <4) at the Interim Assessment visit (Day 7 to 14).
- Proportion of mITT patients with therapeutic cure at the Interim Assessment visit (Day 7 to 14).

Analysis of the secondary endpoints was to use the same method as that of the primary endpoint.

The PP population was to be used to perform sensitivity analyses of the above primary and secondary efficacy analyses. Patients in the PP population without a clinical cure assessment at the TOC visit (Day 21 to 30) were to be excluded from the PP analyses.

Pharmacokinetic Analysis

The following PK parameters were to be summarized for the PK subset population to assess plasma and vaginal clindamycin levels on Days 1 to 7:

(1) Minimum concentration.
(2) Maximum concentration.
(3) Area under the curve (AUC_{0-t}), where t is the last time-point with measurable concentration).
(4) Time to maximum concentration.
(5) Elimination half-life.

Descriptive summaries of plasma and vaginal clindamycin levels were to be presented for each timepoint.

Safety Analyses

Descriptions of AEs were to include the date of onset, the date the AE ended, the maximum severity of the AE, relationship to study drug, seriousness, any action taken, and the outcome.

All treatment-emergent adverse events occurring during the study were to be recorded and classified on the basis of Medical Dictionary for Regulatory Activities terminology. Treatment-emergent AEs are those AEs with an onset at the time of, or after the application of study drug. All reported treatment-emergent adverse events were to be summarized by treatment group, system organ class and preferred term. Adverse events summaries also included severity, relationship to study drug, and seriousness. When summarizing events by causality and severity, each patient was to be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification. In addition, a list of patients who had a serious adverse event or who prematurely discontinued from the study due to an AE was to be provided.

Changes from baseline and shifts from baseline were to be summarized for safety laboratory results. A listing that displays all out-of-range laboratory test results was also to be provided.

Local site reactions were to be summarized at each visit.

Interim Analysis

No interim analysis was planned.

Sample Size Justification

The sample size calculations were to be performed using SAS® version 9.4 for the two-group chi-squared test. This test was expected to provide approximately the same power as the Cochran-Mantel-Haenszel test stratified by analysis center and race. A sample size of 188 DARE-BV1 versus 94 placebo patients would have 90% power to detect a statistically significant difference at a significance level of 0.05 (two-tailed) under the assumption that the clinical cure rates would be 55% and 30% for DARE-BV1 and placebo, respectively. This sample size assumed that 35% of randomized patients would not be in the mITT population.

16. Efficacy: Additional Information and Assessment

Baseline demographic and clinical characteristics for the ITT population are summarized in Table 37. The baseline characteristics were similar between treatment arms. The median age was 35 years. Only one subject was between 12 and 17 years of age (age 15 years and randomized to DARE-BV1) and no subject was older than 59 years. The majority of the subjects were black or African American (56.0%) and non-Hispanic (74.5%). The majority of subjects had a Nugent score between 7 and 10. Approximately 89% of subjects had a history of at least one previously diagnosed BV episode in their lifetime. Approximately 19% of subjects reported having more than three BV episodes in the past 12 months.

Table 37. Baseline Demographic and Clinical Characteristics, ITT Population, DARE-BV1-001

Characteristic	DARE-BV1 (N=204)	Placebo (N=103)
Sex, n (%)		
Female	204 (100.0)	103 (100.0)
Age, years		
Mean (SD)	34.6 (8.8)	35.2 (8.9)
Median (minimum, maximum)	34 (15, 56)	35 (19, 59)
Age group (years), n (%)		
≤20	5 (2.5)	1 (1.0)
21 to 30	66 (32.4)	33 (32.0)
31 to 40	84 (41.2)	42 (40.8)
41 to 50	41 (20.1)	20 (19.4)
≥51	8 (3.9)	7 (6.8)
Race, n (%)		
White	82 (40.2)	44 (42.7)
Black/African American	116 (56.9)	56 (54.4)
Other	6 (2.9)	3 (2.9)
Ethnicity, n (%)		
Hispanic	57 (27.9)	21 (20.4)
Non-Hispanic	146 (71.6)	82 (79.6)
Nugent score, n (%)		
0 to 3	13 (6.4)	9 (8.7)
4 to 6	23 (11.3)	15 (14.6)
7 to 10	165 (80.9)	76 (73.8)
Missing	3 (1.5)	3 (2.9)
History of BV, n (%)		
Yes	183 (89.7)	90 (87.4)
No	21 (10.3)	13 (12.6)
Episodes in past 12 months, n (%)		
≤3	166 (81.4)	83 (80.6)
>3	37 (18.1)	20 (19.4)
History, but number not reported	1 (0.5)	0 (0)

Source: Reviewer-conducted analyses using the ADSL, ADMB, and ADFA datasets.
Abbreviations: BV, bacterial vaginosis; ITT, intent-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

17. Clinical Safety: Additional Information and Assessment

Table 38. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial DARE-BV1-001

Treatment-Emergent Adverse Event	DARE-BV1 N=202 n (%)	Placebo N=103 n (%)
Infections and infestations	46 (22.8%)	15 (14.6%)
Vulvovaginal candidiasis	35 (17.3%)	4 (3.9%)
Urinary tract infection	6 (3.0%)	5 (4.9%)
Trichomoniasis	4 (2.0%)	2 (1.9%)
Bacterial vaginosis	3 (1.5%)	3 (2.9%)
Herpes zoster	1 (0.5%)	0 (0.0%)
Genital herpes	1 (0.5%)	0 (0.0%)
COVID-19	1 (0.5%)	0 (0.0%)
Pharyngitis streptococcal	1 (0.5%)	0 (0.0%)
Pelvic inflammatory disease	0 (0.0%)	2 (1.9%)
Pelvic infection	0 (0.0%)	1 (1.0%)
Papilloma viral infection	0 (0.0%)	1 (1.0%)
Vaginal infection	0 (0.0%)	1 (1.0%)
Bacterial vulvovaginitis	0 (0.0%)	1 (1.0%)
Reproductive system and breast disorders	23 (11.4%)	10 (9.7%)
Vulvovaginal pruritus	9 (4.5%)	2 (1.9%)
Vaginal hemorrhage	5 (2.5%)	4 (3.9%)
Vaginal discharge	3 (1.5%)	0 (0.0%)
Vulvovaginal burning sensation	3 (1.5%)	2 (1.9%)
Vulvovaginal erythema	2 (1.0%)	0 (0.0%)
Vulval disorder	1 (0.5%)	0 (0.0%)
Vulva cyst	1 (0.5%)	0 (0.0%)
Pelvic pain	1 (0.5%)	0 (0.0%)
Vulvovaginal discomfort	1 (0.5%)	1 (1.0%)
Vulvovaginal dryness	1 (0.5%)	0 (0.0%)
Menstruation irregular	1 (0.5%)	0 (0.0%)
Cervical friability	0 (0.0%)	1 (1.0%)
Cervical dysplasia	0 (0.0%)	1 (1.0%)
Cervix disorder	0 (0.0%)	1 (1.0%)
Gastrointestinal disorders	6 (3.0%)	2 (1.9%)
Diarrhea	2 (1.0%)	1 (1.0%)
Abdominal pain	2 (1.0%)	1 (1.0%)
Abdominal pain lower	1 (0.5%)	0 (0.0%)
Constipation	1 (0.5%)	0 (0.0%)
Gastroesophageal reflux disease	1 (0.5%)	0 (0.0%)
Nervous system disorders	2 (1.0%)	1 (1.0%)
Anosmia	1 (0.5%)	0 (0.0%)
Ageusia	1 (0.5%)	0 (0.0%)
Somnolence	1 (0.5%)	0 (0.0%)
Headache	1 (0.5%)	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	2 (1.0%)	0 (0.0%)
Cough	1 (0.5%)	0 (0.0%)
Nasal congestion	1 (0.5%)	0 (0.0%)

Treatment-Emergent Adverse Event	DARE-BV1 N=202 n (%)	Placebo N=103 n (%)
Skin and subcutaneous tissue disorders	2 (1.0%)	3 (2.9%)
Miliaria	1 (0.5%)	0 (0.0%)
Rash papular	1 (0.5%)	0 (0.0%)
Intertrigo	0 (0.0%)	1 (1.0%)
Skin lesion	0 (0.0%)	1 (1.0%)
Drug eruption	0 (0.0%)	1 (1.0%)
Blood and lymphatic system disorders	2 (1.0%)	0 (0.0%)
Lymphadenopathy	1 (0.5%)	0 (0.0%)
Anemia	1 (0.5%)	0 (0.0%)
Investigations	1 (0.5%)	2 (1.9%)
Blood creatinine increased	1 (0.5%)	0 (0.0%)
Blood pressure increased	0 (0.0%)	1 (1.0%)
Alanine aminotransferase increased	0 (0.0%)	1 (1.0%)
Injury, poisoning and procedural complications	1 (0.5%)	0 (0.0%)
Skin laceration	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions	1 (0.5%)	0 (0.0%)
Pyrexia	1 (0.5%)	0 (0.0%)
Ear and labyrinth disorders	1 (0.5%)	0 (0.0%)
Ear pain	1 (0.5%)	0 (0.0%)
Surgical and medical procedures	1 (0.5%)	0 (0.0%)
Tooth extraction	1 (0.5%)	0 (0.0%)
Metabolism and nutrition disorders	1 (0.5%)	0 (0.0%)
Type 2 diabetes mellitus	1 (0.5%)	0 (0.0%)

Source: Clinical Reviewer.
Abbreviations: COVID-19, coronavirus disease 2019; N, number of subjects in treatment arm; n, number of subjects with at least one event

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Mechanism of Action

Clindamycin inhibits bacterial protein synthesis by binding to the 23S ribonucleic acid of the 50S subunit of the ribosome and affects peptide chain initiation. Clindamycin may be either bacteriostatic or bactericidal depending on the drug concentration, bacterial species, and size of the inoculum.

Resistance

There are many mechanisms of bacterial resistance to clindamycin; however, resistance to clindamycin is most often caused by modification of certain bases of the 23S ribosomal ribonucleic acid. Cross-resistance between clindamycin and lincomycin is complete. Because the binding sites for these antibacterial drugs overlap, cross-resistance is sometimes observed among lincosamides, macrolides, and streptogramin B.

Macrolide-inducible resistance to clindamycin occurs in some isolates of macrolide-resistant bacteria. Macrolide-resistant isolates of staphylococci and beta-hemolytic streptococci should be screened for induction of clindamycin resistance. Recently, high rates of resistance to clindamycin have developed in some *Bacteroides* spp. that are often associated with BV.

Antimicrobial Activity

Clindamycin has been shown to be active against most isolates of the following microorganisms, which are reportedly associated with BV (see Clinical Studies, Section 14):

- *Atopobium vaginae*
- *Bacteroides* spp.
- *Gardnerella vaginalis*
- *Mobiluncus* spp.
- *Peptostreptococcus anaerobius*
- *Prevotella* spp.

Susceptibility testing: Culture and sensitivity testing are not routinely performed for organisms causing BV.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

No significant issues that affected the interpretation of this review were found.

Routine Prescription Drug User Fee Application inspections were conducted for two clinical investigators, Drs. Nicholson-Uhl (#125) and Perez (#126), in support of this application (NDA 215650). The two inspections covered one clinical study, DARE-BV1-001. Overall, the study appears to have been conducted adequately, and the data generated by these two sites appear acceptable in support of the respective indication.

During the inspections, the primary efficacy endpoint source data for clinical cure (i.e., investigator assessment of vaginal discharge, 10% KOH whiff test, and clue cell percentage) were verified against the Applicant's data line listings for 30 of the 40 subjects randomized at these two sites. No discrepancies were noted. Although certified copies of the Nugent scores used to determine the supportive secondary efficacy endpoint of bacteriological cure were not available at the clinical investigator sites, these certified copies were submitted to the NDA and subsequently verified by this reviewer against the Applicant's data line listings for all 40 randomized subjects at the two sites. No discrepancies were noted.

21. Labeling Summary of Considerations and Key Additional Information

Prescribing Information

General

- Outlined below are the significant changes made to specific sections/subsections in the FULL PRESCRIBING INFORMATION section of the prescribing information (PI) submitted by the Applicant on June 7, 2021.
- HIGHLIGHTS and TABLE OF CONTENTS were revised for consistency with the rest of the PI.

1. INDICATIONS AND USAGE

1.1 Bacterial Vaginosis

- The description of the population in the INDICATIONS AND USAGE section was changed from adult women to females 12 years of age and older.
  - See Section II.7.7.1 for discussion on including females 12 to <18 years of age in the INDICATIONS AND USAGE section.
  - Pregnant or nonpregnant women were not specifically mentioned in the INDICATIONS AND USAGE section.
    One of the relied-upon LDs, Cleocin Vaginal Cream 2% (NDA 050680), is currently approved for the following indication: "CLEOCIN Vaginal Cream 2%, is indicated in the treatment of bacterial vaginosis (formerly referred to as *Haemophilus vaginitis*, *Gardnerella vaginitis*, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis). CLEOCIN Vaginal Cream 2%, can be used to treat non-pregnant women and pregnant women during the second and third trimester. (See CLINICAL STUDIES.)" The Pregnancy section of that labeling states: "Clindamycin vaginal cream should be used during the first trimester of pregnancy only if clearly needed and the benefits outweigh the risks. There are no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy."

    In general, for prescription drug labeling, the adult population is defined as patients 17 years and older and consistent with recently approved drug labeling, includes pregnant women. Because pregnant women are considered part of the adult population, the term, "pregnant women" is generally not specifically mentioned in the INDICATIONS AND USAGE section, unless the drug is approved to treat a specific pregnancy-related condition. Therefore, the INDICATIONS AND USAGE section for XACIATO will omit any mention of pregnant women and instead state: "Treatment of bacterial vaginosis in females 12 years and older"

    In addition, risk information pertinent to use of the drug in pregnancy, is described in the Pregnancy subsection (21 CFR 201.57(c)(9)(i)) in USE IN SPECIFIC POPULATIONS (Section 8), and such risk information is incorporated in other sections of labeling as pertinent (e.g., CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS). Because the level of systemic absorption of clindamycin

vaginal products, including XACIATIO, is considered low, the Pregnancy subsection of XACIATO will include a statement, which is currently absent in the other clindamycin vaginal product labeling, that states that based on the low systemic absorption of XACIATO following the intravaginal route of administration in nonpregnant women, maternal use is not likely to result in significant fetal exposure to the drug.

- See Section II.8.4 for additional discussion of pregnancy.
- The indication statements for other vaginal clindamycin products (Cleocin cream, Cleocin ovules, and Clindesse cream) will be updated to match Xaciato because the same principles regarding removal of the pregnancy information from the indication statement apply to all of these products.

4. CONTRAINDICATIONS

(b) (4)

- Removed the contraindication for (b) (4) added information about IBD and *Clostridioides difficile* infection (CDI) to the CDI Warning and Precaution in Subsection 5.1).
  - Clindamycin increases the risk for CDI and patients with IBD have a higher risk of CDI. However, there may be patients with IBD who may benefit from Xaciato and Xaciato should not be contraindicated for these patients. To inform prescribers about the risk to patients with IBD, information about CDI and IBD was included in the warning about CDI. The other vaginal clindamycin product labeling (Cleocin cream, Cleocin ovules, and Clindesse cream) will be updated to remove this contraindication.

5. WARNINGS AND PRECAUTIONS

5.1. *Clostridioides difficile*-Associated Diarrhea (CDAD)

- Added the following statement to subsection 5.1: “Patients with inflammatory bowel disease, including ulcerative colitis and Crohn’s disease, have a higher risk of developing CDAD.”

5.2. Use with Polyurethane Condoms

- Edited the Warning and Precaution of Xaciato not being compatible with the use of polyurethane condoms, to extend the duration of avoidance from (b) (4) days to 7 days, following treatment with Xaciato.
  - The recommended duration of avoiding polyurethane condoms was increased to 7 days because in the PK study some subjects had detectable vaginal clindamycin levels at 3 to 7 days after administration.

5.3. Vaginal *Candida* Infections

- Added a Warning and Precaution regarding Xaciato resulting in the overgrowth of *Candida* spp. in the vagina resulting in vulvovaginal candidiasis which may require antifungal treatment. This is consistent with the LD (Cleocin vaginal cream).

6. ADVERSE REACTIONS

6.2 Other Clindamycin Formulations

- Edited the Renal System Organ Class to add "acute kidney injury" instead of (b) (4) [redacted] This was added for consistency with recent changes made to other clindamycin drug products.
- Labeling for the clindamycin vaginal cream products (Cleocin cream, Cleocin ovules, and Clindesse cream) will be updated to add acute kidney injury.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy and 8.2 Lactation

- Edited the pregnancy Subsection 8.1 to note that based on the low systemic absorption of Xaciato following intravaginal administration in nonpregnant women, maternal use is not likely to result in significant fetal exposure to the drug.
  - Edited the lactation Subsection 8.2 to note that systemic absorption following intravaginal administration of clindamycin is low; therefore, transfer of clindamycin into breastmilk is likely to be low and adverse effects on the breastfed infant are not expected.
  - See Section II.8.4 for additional discussions regarding pregnancy and lactation.
  - The labeling for the other clindamycin vaginal products (Cleocin cream, Cleocin ovules, and Clindesse cream) will be updated to note that the low systemic exposure of vaginal clindamycin products is not likely to result in significant fetal exposure to the drug.

8.3 Males and Females of Reproductive Potential

- A "Contraception" subheading was added to Subsection 8.3 to include information regarding the use of polyurethane condoms not being compatible with Xaciato use during and for 7 days following treatment with Xaciato.

8.4. Pediatric Use

- Edited the description of the specific pediatric subpopulation in the pediatric use statement to indicate that safety and effectiveness of Xaciato have been established in "females aged 12 years and older" for the treatment of bacterial vaginosis instead of (b) (4) [redacted]
- See Sections II.7.7.1 and II.8.3 for additional discussions regarding the inclusion of female pediatric patients 12 to less than 18 years of age in the Indications and Usage section and the Pediatric Use section.
- Edited the description of the specific pediatric population in the appropriate pediatric use statement to indicate that the safety and effectiveness of Xaciato have not been

established in pediatric patients "younger than 12 years of age" for the treatment of bacterial vaginosis instead of [redacted] (b) (4) ."

- See Section 12 of this review for additional discussions regarding pediatric females less than 12 years of age. The labeling for the other clindamycin vaginal products (Cleocin cream, Cleocin ovules, and Clindesse cream) will be updated to revise the description of the specific pediatric subpopulation in the Pediatric subsection of the labeling.

12. CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

- Added the statement [redacted] (b) (4) " according to the Clinical Pharmacology Section of the Labeling (final guidance) (page 8). The guidance states that if the drug is classified as a prodrug then this designation should also be stated in Subsection 12.3 of the PI.
- This update will be added to other clindamycin products appropriately including the vaginal products (Cleocin cream, Cleocin ovules, and Clindesse cream).

14. CLINICAL STUDIES

- Deleted reference to the [redacted] (b) (4) in the CLINICAL STUDIES section because [redacted] (b) (4) does not add to the interpretation of the results. In addition, the [redacted] (b) (4) was not included in the labeling of other recently approved BV drugs.

22. Postmarketing Requirements and Commitments

Postmarketing commitment: No postmarketing requirements or commitments.

[redacted] APPEARS THIS WAY ON ORIGINAL

23. Financial Disclosure

Table 39. Covered Clinical Studies: DARE-BV1-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
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: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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25. Review Team

Table 40. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Alison Rodgers
Chief, Project Management Staff	Maureen Dillon-Parker, MS, RAC
Nonclinical Reviewer	Kelly Brant, PhD, MPH, DABT
Nonclinical Team Leader	Terry Miller, PhD
Office of Clinical Pharmacology Reviewer(s)	Meng Wang, PhD
Office of Clinical Pharmacology Team Leader(s)	Kunyi Wu, PharmD
Clinical Reviewer	Mukil Natarajan, MD
Clinical Team Leader	Hiwot Hiruy, MD, PhD
Statistical Reviewer	Cheryl Dixon, PhD
Statistical Team Leader	Karen Higgins, ScD
Cross-Disciplinary Team Leader	Hiwot Hiruy MD, PhD
Associate Director for Labeling	Abimbola Adebowale, PhD
Division Director (Pharm/tox)	Hanan Ghantous, PhD
Division Director (OCP)	
Division Director (OB)	
Clinical Team Leader	Peter Kim, MD, MS
Deputy Division Director (Clinical)	Dmitri Iarikov, MD, PhD
Office Director (or designated signatory authority)	

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 41. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dorota Matecka, PhD; Peter Guerrieri, PhD; David Claffey, PhD; Rajan Pragani, PhD; Paresma Patel, PhD; Renee Marcsisin-Rogers, PhD; Paul Dexter, PhD; Jiao Yang, PhD; Steven Frisbee; Anh-Thy Ly, PharmD; Ramesh Gopalaswamy, PhD; David Lewis, PhD
Microbiology	Lynette Berkeley, PhD; Avery Goodwin, PhD
OPDP	Melissa Khashei, PharmD; James Dvorsky, PharmD, RAC
OSI	Cheryl Grandinetti, PharmD; Phillip Kronstein, MD; Kassa Ayalew, MD
OSE/DEPI	Natasha Pratt, PhD
OSE/DMEPA	Deborah Myers, RPh, MBA; Valerie Vaughan, PharmD
OSE/DRISK	N/A
CDRH	Rebecca Dorsey, BS
DPMH	Wenjie Sun, MD; Miriam Dinatale, MD; Lynne Yao, MD
DUOG	Audrey Gassman, MD; Christina Chang, MD, MPH; Marcea Whitaker, MD

Abbreviations: CDRH, Center for Devices and Radiological Health; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatrics and Maternal Health; DRISK, Division of Risk Management; N/A, not applicable; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 42. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Dmitri Iarikov, MD, PhD	OND/OID/DAI	I-III ☐ Authored ☐ Contributed ☒ Approved
Signatory Authority	**Signature:** Dmitri E. Iarikov -S Digitally signed by Dmitri E. Iarikov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000351806, cn=Dmitri E. Iarikov -S Date: 2021.12.03 15:30:45 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Peter Kim, MD, MS	OND/OID/DAI	I-III ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Peter W. Kim -S Digitally signed by Peter W. Kim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Peter W. Kim -S, 0.9.2342.19200300.100.1.1=1300202560 Date: 2021.12.03 14:31:18 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	Abimbola Adebowale, PhD	OND/OID/DAI	III - 21 ☐ Authored ☐ Contributed ☒ Approved
Associate Director for Labeling	**Signature:** Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300141826, cn=Abimbola O. Adebowale -S Date: 2021.12.03 14:25:57 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Hiwot Hiruy, MD, PhD	OND/OID/DAI	I-III ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Hiwot Hiruy -S Digitally signed by Hiwot Hiruy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hiwot Hiruy -S, 0.9.2342.19200300.100.1.1=2001757339 Date: 2021.12.03 13:22:54 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Mukil Natarajan, MD	OND/OID/DAI	2.1, 3, 4, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 8.3, 8.4, 10, 11, 17, 20, 21, 23 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Mukilan Natarajan -S	Digitally signed by Mukilan Natarajan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011788542, cn=Mukilan Natarajan -S Date: 2021.12.03 12:37:43 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Cheryl Dixon, PhD	OB/DBIV	6.2, 6.3.1, 6.3.2, 15, 16 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Cheryl A. Dixon -S	Digitally signed by Cheryl A. Dixon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300115195, cn=Cheryl A. Dixon -S Date: 2021.12.03 11:46:09 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Karen Higgins, ScD	OB/DBIV	6.2, 6.3.1, 6.3.2, 15, 16 ☐ Authored ☐ Contributed ☒ Approved
Supervisor	**Signature:** Karen M. Higgins -S	Digitally signed by Karen M. Higgins -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300117310, cn=Karen M. Higgins -S Date: 2021.12.03 12:17:17 -05'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Kelly Brant, PhD, MPH, DABT	OND/DAI/DPTID	II. 7.1, II. 8.4, III.13 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Kelly A. Brant -S	Digitally signed by Kelly A. Brant -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kelly A. Brant -S, 0.9.2342.19200300.100.1.1=2001539497 Date: 2021.12.03 13:02:51 -05'00'	

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Terry Miller, PhD	OND/DAI/DPTID	II 7.1, II 8.4, III 13 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Terry J. Miller -S Digitally signed by Terry J. Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S Date: 2021.12.03 12:31:47 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Dorota Matecka, PhD	OPQ/DNDP 1	II - 9, 9.1 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Dorota M. Matecka -S		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Meng Wang, PhD	OTS/OCP/DIDP	5, 14 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Meng Wang -S		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Kunyi Wu, PharmD	OTS/OCP/DIDP	5, 14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Kunyi Wu -S Digitally signed by Kunyi Wu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kunyi Wu -S, 0.9.2342.19200300.100.1.1=2000594958 Date: 2021.12.03 14:07:30 -05'00'		

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Clinical Microbiology	Lynette Berkeley, PhD, MT (ASCP)	OND/OID/DAI	5.1, 18 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	**Signature:** Lynette Berkeley -S Digitally signed by Lynette Berkeley -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000266422, cn=Lynette Berkeley -S Date: 2021.12.03 13:39:57 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Microbiology	Avery Goodwin, PhD	OND/OID/DAI	5.1, 18 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211785, cn=Avery C. Goodwin -S Date: 2021.12.03 13:54:49 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Alison Rodgers	OND/ORO/DRO-ID/DAI	III-12 ☒ Authored ☐ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Alison K. Rodgers -S Digitally signed by Alison K. Rodgers -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300236199, cn=Alison K. Rodgers -S Date: 2021.12.03 14:02:07 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Maureen Dillon-Parker, MS, RAC	OND/ORO/DRO-ID/DAI	III-12 ☐ Authored ☒ Contributed ☒ Approved
Supervisor	**Signature:** Maureen P. Dillon Parker -S Digitally signed by Maureen P. Dillon Parker -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042254, cn=Maureen P. Dillon Parker -S Date: 2021.12.03 13:30:51 -05'00'		

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