1 TITLE PAGE

Protocol Number:	DARE-BV1-001
Study Title:	A Phase 3 Multi-center, Double-blind, Placebo-controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis
Development Phase:	Phase 3
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Version Number:	4.0
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This study will be carried out in compliance with the International Council for Harmonisation (ICH) E6 (R2) guidance on Good Clinical Practice (GCP) and the United States (U.S.) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312).

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event
BV	Bacterial Vaginosis
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel test
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HEC	Hydroxyethylcellulose
HPV	Human Papillomavirus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
KOH	Potassium Hydroxide
LTFU	Lost to Follow-Up
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-to-Treat
N	Number of Patients
NAAT	Nucleic Acid Amplification Test
PK	Pharmacokinetics
PKS	Pharmacokinetics Subset (population)
PP	Per-Protocol
QD	Daily (Latin: Quaque Die)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
spp.	Species Pluralis (i.e., multiple species in a given genus)
STI	Sexually-transmitted Infections
TEAE	Treatment Emergent Adverse Events
TOC	Test of Cure
U.S.	United States
WHO-DD	World Health Organization Drug Dictionary

4 PROTOCOL SUMMARY

4.1 SYNOPSIS

Name of Sponsor/Company:

Daré Bioscience, Inc.

Name of Investigational Product:

Clindamycin phosphate vaginal gel, 2% (DARE-BV1)

Name of Active Ingredient:

Clindamycin phosphate

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 will be up to approximately 1 month:

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

For patients in the pharmacokinetics (PK) subset only, there will be additional blood draws at Visit 1 (Day 1) as well as 5 additional visits between Visit 1 and Visit 2 (Visits PK1-PK5 on Days 2 through 6).

Phase of development: 3

Objectives:

Primary:

Assess the efficacy of DARE-BV1 for the treatment of bacterial vaginosis (BV) in postmenarchal females.

Secondary:

Assess the safety and acceptability of DARE-BV1.

Study Design:

This is a multicenter, randomized, double-blind, placebo-controlled study of DARE-BV1 (clindamycin phosphate vaginal gel, 2%) (daily [QD] × 1 day) compared to placebo vaginal gel (hydroxyethylcellulose [HEC] Universal Placebo Gel) (QD × 1 day) for the treatment of BV. Patients will be evaluated at 3 time points: a Day 1 Screening/Randomization visit, a Day 7-14 Interim

Assessment visit, and a Day 21-30 Test of Cure [TOC] visit). Patients who discontinue prematurely from the study will receive a safety follow-up phone call between Day 21-30. The total study duration will be up to approximately 1 month for each individual 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) will be collected/evaluated. Signs and symptoms of BV will be evaluated, including color, odor, and consistency of vaginal discharge, plus vulvovaginal itching and irritation will be assessed. Additionally, the following samples/tests will be 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 (NAATs) for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, OSOM® test for *Trichomonas vaginalis,* blood sample for chemistry and hematology, and urinalysis.

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

Eligible patients will be randomly assigned via Interactive Response Technology (IRT) 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 will be applied intravaginally within 1 day of randomization.

The patients will return to the clinic for Visit 2 on Day 7-14 for the Interim Assessment. A third and final visit will be conducted at Day 21-30 for TOC. Similar to the requirement at randomization, patients should not be 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 the Visit 2 (Day 7-14) and Visit 3 (Day 21–30) visits, the Investigator will perform gynecological examinations and collect 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 the 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 will be evaluated at each visit. Post-treatment blood chemistry and hematology assessments will be obtained at the TOC Visit (Visit 3, Day 21-30). Repeat testing for *N. gonorrhea, C. trachomatis, T. vaginalis* or *Candida* species may be obtained 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 will occur at each visit. A review of patient-reported and Investigator-assessed local site reactions will occur at each visit after randomization and treatment.

Approximately 20 patients at selected sites (2-4 sites are anticipated) will participate in a PK study. The patients in this subset will apply the study drug during Visit 1 at the study clinic and will have blood draws for plasma clindamycin assessment taken at 0 hours (pre-dose) and then at 2, 4, 6, and 8 hours (± 15 minutes) post-dose, as well as at 24, 48, 72, 96, 120, and 144 hours (±2 hours) post-dose

(Days 2-7). In addition, samples for vaginal clindamycin concentrations will be collected on Days 1-7 (with the Day 1 sampling schedule starting pre-dose). For these patients, the assessments for the Interim Assessment (Day 7-14) visit may be done 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 21-30). 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 21-30). If other BV treatment is prescribed at Visit 3, then the patient should either be followed by the study doctor (if the patient is regularly treated at their clinic), or referred back to their local health care 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 is for all patients to complete the study, regardless of whether additional BV treatment, yeast treatment or other anti-microbial therapy is required prior to completion of the final TOC Visit (Visit 3, Day 21-30). Patients who discontinue prematurely from the study for any reason will receive a Safety Follow-up phone call between Study Days 21-30 to assess the status of BV symptoms, AEs, and medication usage.

Primary Efficacy Endpoint:

- The primary efficacy endpoint is the proportion of patients with ***Clinical Cure*** at the TOC visit (Day 21-30). Clinical Cure is 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 the saline wet mount.

Secondary Efficacy Endpoints:

- Proportion of patients with ***Bacteriological Cure*** at the TOC visit (Day 21-30). Bacteriological Cure is defined as a Nugent score < 4.
- Proportion of patients with ***Therapeutic Cure*** at the TOC visit (Day 21-30). Therapeutic Cure is 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 7-14).
- Proportion of patients with ***Bacteriological Cure*** (Nugent score < 4) at the Interim Assessment visit (Day 7-14).
- Proportion of patients with ***Therapeutic Cure*** at the Interim Assessment visit (Day 7-14).

Safety and Acceptability Assessments:

- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- OSOM® test for *Trichomonas vaginalis*
- NAATs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
- Clinical and microscopic assessment for vulvovaginal candidiasis
- Vaginal culture for *Candida* species

- Review of treatment-emergent adverse events (TEAEs) 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 1-7
- Vaginal clindamycin concentration levels for Days 1-7

Number and types of patients (planned):

Approximately 282 patients will be enrolled.

Criteria for Inclusion:

Diagnosis and Main Eligibility Criteria:

Patients with a clinical diagnosis of BV (see below) at the Screening/Randomization Visit who meet the following eligibility criteria may participate in the study:

Inclusion Criteria:

1. Patients must provide written informed consent prior to any study-related procedures being performed. Patients from 12 through 17 years old may participate where permitted by applicable local regulations and Institutional Review Board (IRB) 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 the saline wet mount
    c. Vaginal secretion pH of > 4.5
    d. A fishy odor of the vaginal discharge with the 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 throughout the first 7 days following treatment. Non-pregnant 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 21-30).
5. This trial will enroll pregnant women; however, non-pregnant 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 (IUDs), contraceptive implants under the skin, patches or injections, and non-polyurethane 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 1 full cycle (e.g., 4 to 8 weeks) prior to study drug application. Injectable or implanted contraceptives (e.g., Depo-Provera, Nexplanon, or hormonal IUD) must have been injected/inserted at least 7 days prior to study drug application.

Patients who are not of childbearing potential will not need a urine pregnancy test prior to randomization or at subsequent visits. The patient is considered to be of non-child bearing potential if one of the following is 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. Non-surgical permanent sterilization procedure performed at least 3 months prior to study drug application.

6. Patients must be willing to refrain from the use of all intra-vaginal products (e.g., douches, feminine deodorant sprays, condoms, spermicides, vaginal moisturizers or lubricants, tampons, vaginal birth control rings [e.g., NuvaRing®], and diaphragms) through the first 7 days at a minimum, and ideally through Visit 3 (Day 21-30) 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 (HPV), *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 *Clostridium 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 HPV 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%) will be supplied in tubes with accompanying applicators. To dispense the product, the patient will screw 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) will be applied intravaginally as a single dose.

Reference Therapy, Dose, and Mode of Administration:

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

Statistical Analyses:

All statistical processing will be performed using SAS®, Version 9.4, or later. Continuous variables will be summarized with number of patients (N), mean, median, standard deviation (SD), minimum (Min), and maximum (Max). Categorical variables will be summarized with frequency counts and percentages.

All efficacy analyses will be conducted using a 2-sided test at an alpha level of 0.05. The primary efficacy analyses will be conducted on the modified intent-to-treat (mITT) population. Additionally, efficacy analyses will be performed on the per-protocol (PP) population and will be considered supportive. Safety analyses will be performed on the Safety population. Patients will be analyzed according to the treatment to which they were randomized for intent-to-treat (ITT) and mITT analyses, regardless of actual treatment received. For all other analysis populations, patients will be analyzed according to the treatment they received.

Populations:

Intent-to-Treat (ITT): All randomized patients

Safety: All ITT population patients who applied study drug

Pharmacokinetic Subset (PKS): All Safety population patients who are enrolled into the PK subset

Modified Intent-to-Treat (mITT): All Safety population patients except those excluded due to demonstrating 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 are determined to have a baseline Nugent score of < 7. If the Nugent score at baseline is missing, then the patient is excluded from the mITT population.

Per-Protocol (PP): The PP population will include patients from the mITT population who either receive other BV therapy during the study for any reason, or meet the following criteria:

1. Meet all 4 Amsel's criteria at screening
2. Apply study drug within 1 day of randomization
3. Do not use a prohibited medication prior to the Day 21-30 visit
4. Attend the Day 21-30 visit
5. Have no other major protocol violations that impact the primary or secondary endpoints.

For the mITT and PP populations, if the patient receives other BV therapy for any reason, the patient will be included in the analysis as a treatment failure for all visits on or after receipt of the other therapy. Patients will be excluded from the PP population if they receive study treatment that was not

the treatment to which they were randomized. A review of the data will 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:

All efficacy endpoints will 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 21-30 will be analyzed for the mITT population with a Cochran-Mantel-Haenszel (CMH) test stratified by study center and race (African-American/Black versus all others). The method for handling of patients in the mITT analysis without a Clinical Cure result at Day 21-30 will be described in the final Statistical Analysis Plan.

Secondary Efficacy Analyses:

Hypothesis testing for the secondary efficacy endpoints will 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 21-30).
- Proportion of mITT patients with Therapeutic Cure at the TOC visit (Day 21-30).
- Proportion of mITT patients with Clinical Cure (defined above) at the Interim Assessment visit (Day 7-14).
- Proportion of mITT patients with Bacteriological Cure (Nugent score < 4) at the Interim Assessment visit (Day 7-14).
- Proportion of mITT patients with Therapeutic Cure at the Interim Assessment visit (Day 7-14).

Analysis of the secondary endpoints will follow the same method as the analysis of the primary endpoint.

The PP population will 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 21-30) will be excluded from the PP analyses.

Pharmacokinetic Analysis:

The following PK parameters will be summarized for the PKS population to assess plasma and vaginal clindamycin levels for Days 1-7:

1. minimum concentration (C_{min})
2. maximum concentration (C_{max})
3. area under the curve (AUC_{0-t}), where t is the last time-point with measurable concentration)
4. time to maximum concentration (T_{max})
5. elimination half-life ($t_{1/2}$)

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

Safety Analyses:

Descriptions of AEs will 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 TEAEs occurring during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs are those AEs with an onset at the time of, or after the application of study drug. All reported TEAEs will be summarized by treatment group, system organ class and preferred term. Adverse events summaries will also include severity, relationship to study drug, and seriousness. When summarizing events by causality and severity, each patient will 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 (SAE) or who prematurely discontinued from the study due to an AE will be provided.

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

Local site reactions will be summarized at each visit.

Interim Analysis:

No interim analyses are planned.

Sample Size Justification:

The sample size calculations were performed using SAS® version 9.4 for the 2-group chi-square test. It is expected that this test will provide approximately the same power as the CMH test stratified by analysis center and race. A sample size of 188 DARE-BV1 versus 94 placebo patients will have 90% power to detect a statistically significant difference at a significance level of 0.05 (2-tailed) under the assumption that the clinical cure rates will be 55% and 30% for DARE-BV1 and placebo, respectively. This sample size assumes 35% of randomized patients will not be in the mITT population.

4.2 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Safety Follow-up Phone Visit**	**Early Discontinuation**
Visit Name	**Screening/ Randomization**	**Interim Assessment**	**Test of Cure (TOC)**	**(FU after Early Discontinuation)[1] +5 days**	
Study Day(s)	**1**	**7-14**	**21-30**	**21-30**	
Written informed consent administration	X				
Demographics	X				
Medical, gynecological, contraceptive, & relevant sexual history[2]	X				
Height	X				
Weight	X				
Vital signs	X	X	X		X
Concomitant medications	X	X	X	X	X
Adverse events	X	X	X	X	X
Urine pregnancy test[3]	X	X	X		X
Urinalysis[4]	X	X	X		X
Hematology/chemistry	X		X		X
Physical examination[5]	X		X		X
Pelvic examination[6]	X	X	X		X
Assessment of local site reactions[7]	X	X	X		X
Amsel's criteria assessments:					
-Vaginal discharge evaluation	X	X	X		X
-KOH whiff test	X	X	X		X
-Clue cells (wet mount)	X	X	X		X
-Vaginal secretion pH	X	X	X		X
Signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation[8]	X	X	X	X	X
KOH wet mount for microscopic yeast assessment[9]	X	X	X		X
Vaginal culture for *Candida* species[10]	X				
Collect sample/prepare slides for Nugent score[10]	X	X	X		X

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Safety Follow-up Phone Visit**	
Visit Name	**Screening/ Randomization**	**Interim Assessment**	**Test of Cure (TOC)**	**(FU after Early Discontinuation)[1] +5 days**	**Early Discontinuation**
Study Day(s)	**1**	**7-14**	**21-30**	**21-30**	
Perform OSOM® test for *Trichomonas vaginalis*[10]	X				
Collect samples for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* NAATs[10]	X				
Review eligibility criteria	X				
Randomization	X				
Review of eDiary	X	X	X		X
Dispense study drug and instructions	X				
Collect study drug and perform compliance assessment[11]		X			
Record treatment application date		X			
Acceptability Questionnaire		X	X		X

Abbreviations: BV = bacterial vaginosis; eDiary = electronic diary; FU = follow-up; KOH = potassium hydroxide; NAAT = nucleic acid amplification test; TOC = Test of Cure

Notes

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 BV therapy should not be initiated until the patient has completed the final TOC Visit (Visit 3, Day 21-30). 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 21-30). If other treatment is prescribed at Visit 3, then the patient should either be followed by the study doctor (if the patient is regularly treated at their clinic), or be referred back to their local health care 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.

[1] Patients who are discontinued early from the study will be contacted by phone between study Day 21-30 to assess BV symptoms, adverse events and concomitant medications.
[2] For medical, gynecological, contraceptive, and relevant sexual history, the recorded information will include: acute and chronic history of medical and gynecological conditions (including history of BV), smoking, illicit drug and alcohol use history, menstrual cycle history (start date of last menstrual cycle and expected timing of next menses will be collected), medically relevant sexual history including history of sexually-transmitted infections (STIs), current sexual activity, previous/current contraceptive use, and pregnancy history.
[3] Pregnancy testing via urine human chorionic gonadotropin (hCG) testing will be performed for each patient, unless patient is of non-child-bearing potential as defined within Inclusion Criterion #5, at each visit (serum hCG testing will be done only if deemed necessary by the Investigator).
[4] At all visits an in-clinic urine dipstick will be performed. At Visit 1, Visit 3, and the Early Discontinuation visit a central laboratory urinalysis will also be performed.
[5] A complete physical examination should be performed at Visit 1; at Visit 3 and at the Early Discontinuation visit (if applicable), a directed physical examination should be performed in accordance with the Investigator's judgment. Rectal and breast examinations are not required for the complete or directed physical examinations.

[6] Pelvic examination will include a vaginal wall inspection as well as an examination of the cervix and will include assessment and appropriate reporting of any abnormalities, and confirmation that all findings are consistent with BV, versus *Candidiasis* or other causes of the patient's vaginal signs or symptoms.
[7] A review of patient-reported and Investigator-assessed local site reactions will occur at each visit after randomization and treatment. A baseline assessment will be recorded for all subjects during Visit 1 Screening assessments.
[8] The color, odor, and consistency of vaginal discharge are to be assessed as part of the assessment of the Amsel Criteria, and the presence of vulvovaginal itching and irritation are to be assessed as part of the assessment of Local Site Reactions.
[9] The microscopic yeast assessment may be done on the same sample obtained for the 10% KOH whiff test. A swab of the vaginal pool should be utilized for both assessments.
[10] Diagnostic assessments for *Candida spp*, *C. trachomatis, N. gonorrhoeae*, or *T. vaginalis* may be repeated after baseline if changes in the patient's clinical condition warrant re-testing. Full instructions for the collection of all samples, including the slides for Nugent scoring, will be provided in the laboratory procedures manual.
[11] Perform compliance assessment by weighing both the dispensed and returned tubes and recording the weights in the eCRF.

Table 2: Schedule of Assessments for Pharmacokinetic Subset

Visit	**Visit 1**	**Visits PK1-PK5**	**Visit 2**	**Visit 3**	**Safety Follow Up Phone Visit**	**Early Discontinuation**
Visit Name	**Screening/ Randomization**	**PK Draws *(PK Subset Only)***	**Interim Assessment**	**Test of Cure (TOC)**	**FU after Early Discontinuation)[1] +5 days**	
Study Day(s)	**1**	**2, 3, 4, 5, 6**	**7-14**	**21-30**	**21-30**	
Written informed consent administration	X					
Demographics	X					
Medical, gynecological, contraceptive, & relevant sexual history[2]	X					
Height	X					
Weight	X					
Vital signs	X		X	X		X
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Urine pregnancy test[3]	X		X	X		X
Urinalysis[4]	X		X	X		X
Hematology/chemistry	X			X		X
Physical examination[5]	X			X		X
Pelvic examination[6]	X		X	X		X
Assessment of local site reactions[7]	X		X	X		X
Amsel's criteria assessments:						
-Vaginal discharge evaluation	X		X	X		X
-KOH whiff test	X		X	X		X
-Clue cells (wet mount)	X		X	X		X
-Vaginal secretion pH	X		X	X		X
Signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation[8]	X		X	X	X	X
Collect sample for KOH wet mount for microscopic yeast assessment[9]	X	X	X	X		X
Vaginal culture for *Candida* species[10]	X					
Collect samples/prepare slides for Nugent score[10]	X		X	X		X
OSOM® test for *Trichomonas vaginalis*[10]	X					
Collect swabs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* NAATs[10]	X					

Visit	**Visit 1**	**Visits PK1-PK5**	**Visit 2**	**Visit 3**	**Safety Follow Up Phone Visit**	**Early Discontinuation**
Visit Name	**Screening/ Randomization**	**PK Draws *(PK Subset Only)***	**Interim Assessment**	**Test of Cure (TOC)**	**FU after Early Discontinuation)[1] +5 days**	
Study Day(s)	**1**	**2, 3, 4, 5, 6**	**7-14**	**21-30**	**21-30**	
Review eligibility criteria	X					
Randomization	X					
Review of eDiary	X	X	X	X		X
Dispense study drug and instructions	X					
Collect study drug and perform compliance assessment[11]			X			
Record treatment application date			X			
Acceptability Questionnaire			X	X		X
Collect samples for clindamycin plasma level assessment *(PK subset only)*	X *(for PK subset only)*	X *(for PK subset only)*	X *(for PK subset only on Day 7)*			X *(for PK subset only if within first 7 days)*
Collect samples for vaginal clindamycin concentration *(PK subset only)*	X *(for PK subset only)*	X *(for PK subset only)*	X *(for PK subset only on Day 7)*			X *(for PK subset only, if applicable)*

Abbreviations: BV = bacterial vaginosis; eDiary = electronic diary; FU = follow-up; KOH = potassium hydroxide; NAAT = nucleic acid amplification test; PK = pharmacokinetic; TOC = Test of Cure

Notes

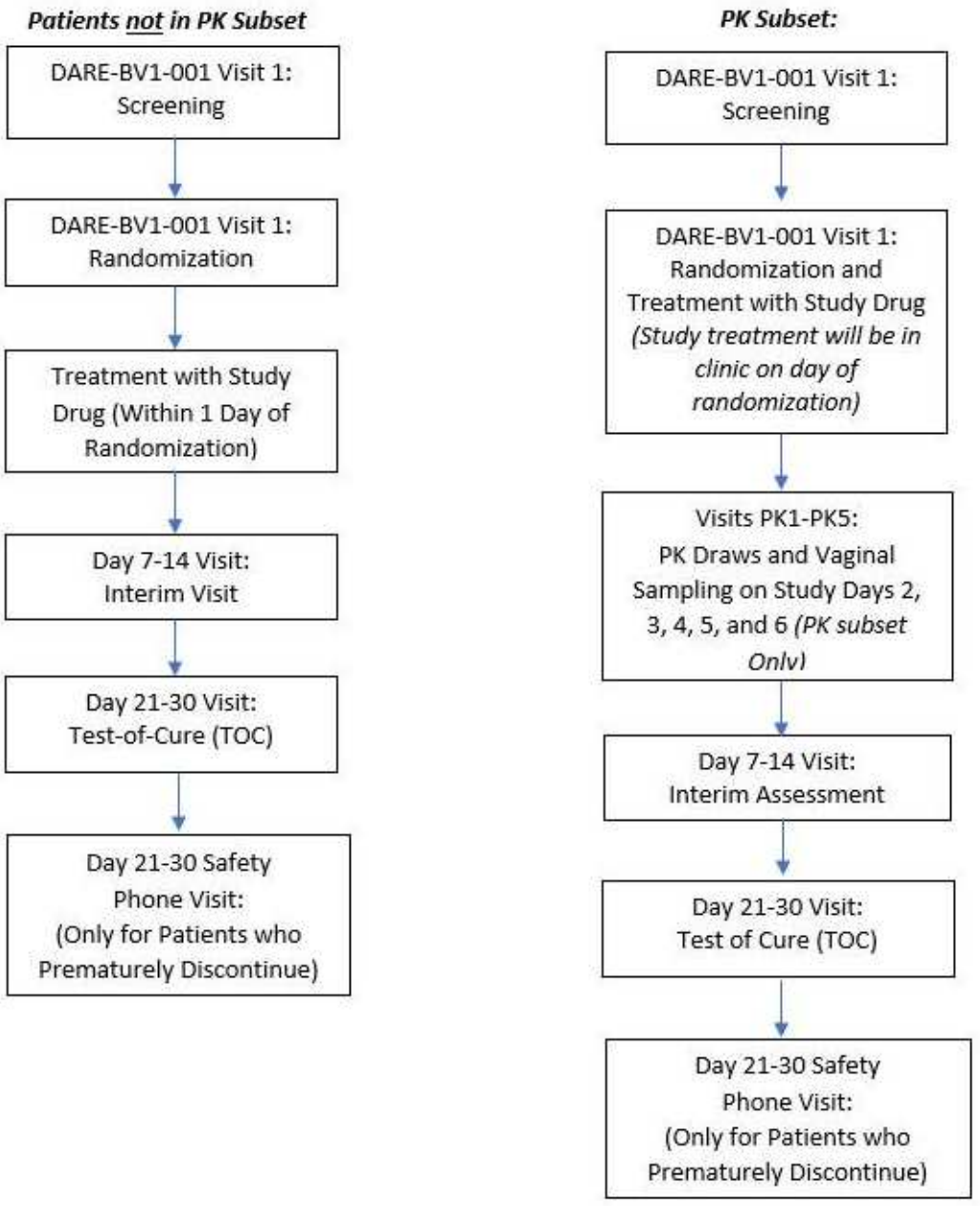
If necessary due to persistent symptoms of BV, patients may be offered other BV treatment prior to completion of the study; however, whenever feasible, other BV therapy should not be initiated until the patient has completed the final TOC Visit (Visit 3, Day 21-30). If initiated prior to Visit 3, then the patient should remain in the study and return to the clinic for the final TOC Visit (Visit 3, Day 21-30). If other treatment is prescribed at Visit 3, then the patient should either be followed by the study doctor (if the patient is regularly treated at their clinic), or be referred back to their local health care 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 additional medications received for treatment of BV should be recorded as concomitant medications.

[1] Patients who are discontinued early from the study will be contacted by phone between study Day 21-30 to assess BV symptoms, adverse events and concomitant medications.
[2] For medical, gynecological, contraceptive, and relevant sexual history, the recorded information will include: acute and chronic history of medical and gynecological conditions (including history of BV), smoking, illicit drug and alcohol use history, menstrual cycle history (start date of last menstrual cycle and expected timing of next menses will be collected), medically relevant sexual history including history of sexually-transmitted infections (STIs), current sexual activity, previous/current contraceptive use, and pregnancy history.

[3] Pregnancy testing via urine human chorionic gonadotropin (hCG) testing will be performed for each patient, unless patient is of non-childbearing potential as defined in Inclusion Criterion #5, at each visit (serum hCG testing will be done only if deemed necessary by the Investigator).
[4] At all visits an in-clinic urine dipstick will be performed. At Visit 1, Visit 3, and the Early Discontinuation visit a central laboratory urinalysis will also be performed.
[5] A complete physical examination should be performed at Visit 1; at Visit 3 and at the Early Discontinuation visit (if applicable), a directed physical examination should be performed in accordance with the Investigator's judgment. Rectal and breast examinations are not required for the complete or directed physical examinations.
[6] Pelvic examination will include a vaginal wall inspection as well as an examination of the cervix and will include assessment and appropriate reporting of any abnormalities, and confirmation that all findings are consistent with BV, versus *Candidiasis* or other causes of the patient's vaginal signs or symptoms.
[7] A review of patient-reported and Investigator-assessed local site reactions will occur at each visit after randomization and treatment. A baseline assessment will be recorded for all subjects during Visit 1 Screening assessments.
[8] The color, odor, and consistency of vaginal discharge are to be assessed as part of the assessment of the Amsel Criteria, and the presence of vulvovaginal itching and irritation are to be assessed as part of the assessment of Local Site Reactions.
[9] The microscopic yeast assessment may be done on the same sample obtained for the 10% KOH whiff test. A swab of the vaginal pool should be utilized for both assessments.
[10] Diagnostic assessments for *Candida spp*, *C. trachomatis, N. gonorrhoeae*, or *T. vaginalis* may be repeated after baseline if changes in the patient's clinical condition warrant re-testing. Full instructions regarding the collection of all samples, including the slides for Nugent scoring, will be included in the laboratory procedures manual.
[11] Perform compliance assessment by weighing both the dispensed and returned tubes and recording the weights in the eCRF.

Figure 1: Study Flow Charts



5 INTRODUCTION

5.1 STUDY RATIONALE AND BACKGROUND

Bacterial vaginosis (BV) is the most common vaginal infection in postmenarchal females of childbearing age. It is a condition in which there is excess growth of certain types of bacteria within the vagina. Recent descriptions have identified in particular the overgrowth of *Gardnerella vaginalis* and *Atopobium vaginae*. This overgrowth affects the normal balance of bacteria within the vagina and can lead to symptoms that include:

- A thin white or gray vaginal discharge
- Pain, itching, or burning in the vagina
- A strong fish-like odor, especially after sex
- Burning when urinating
- Itching around the outside of the vagina

The causes of BV are not fully understood. It is known that BV is more common in sexually active women, but it is not known how sex contributes to BV (Hay, 2014; Center for Disease Control, 2017).

In addition to its symptoms, there is some evidence that BV may contribute to pelvic inflammatory disease, preterm birth, and higher risk of acquisition of sexually transmitted infections (Center for Disease Control, 2017; Sobel & Sobel, 2015; Taylor, 2013).

Currently, in the United States (U.S.), oral and intravaginal metronidazole, intravaginal clindamycin, oral tinidazole, and oral secnidazole are available for the treatment of BV.

DARE-BV1 is a thermosetting bioadhesive intravaginal gel formulated with 2% clindamycin phosphate designed to release the active ingredient for an extended period of time (Mondal, 2011). The extended period of time is approximately 7 days, based on in vitro data, and will be better defined in this study with the pharmacokinetic (PK) subset. Research has shown that effective drug delivery is essential to optimizing drug therapy for BV. Because of its chemical composition, DARE-BV1 is designed as non-toxic and should not compromise condoms or diaphragms.

DARE-BV1 is a viscous solution that undergoes solution to gel (sol-to-gel) transition at body temperature. This property allows the product to remain at the site of vaginal infection. By the process of "reverse thermal gelation," the viscosity of the base matrix increases from room temperature when exposed to body temperature.

Clindamycin has been found effective against organisms usually associated with BV such as *Bacteroides* species (spp.), *Peptococcus* spp., *Gardnerella vaginalis*, *Mobiluncus* spp., and *Mycoplasma hominis*. Clindamycin can be classified as a time-dependent antibiotic for which maximizing the exposure time and the amount of drug is recommended to improve efficacy. Topical application, safety, and efficacy of vaginally delivered clindamycin phosphate have been widely demonstrated in published literature (e.g., Donders, 2014).

DARE-BV1, formulated with clindamycin, is designed to produce a prolonged duration of exposure to clindamycin at the site of infection.

DARE-BV1 has been evaluated in a fertility and early embryonic development to implantation study in rats (Segment 1 reproductive toxicology). It has also been tested in embryo-fetal development toxicity and toxicokinetic studies in rats and rabbits (Segment 2 reproductive toxicology). No adverse outcomes were noted in these studies. Based on these findings, the administration of DARE-BV1 to pregnant

women is justified. Therefore, patients who are known to be pregnant at the time of screening (and who satisfy all entry criteria) will be allowed to enroll in the study.

5.2 RISK/BENEFIT ASSESSMENT

5.2.1 Known Potential Risks/Benefits

DARE-BV1 clindamycin phosphate vaginal gel, 2%, is contraindicated in patients with a prior history of hypersensitivity to clindamycin or other lincosamides or other ingredients of the formulation.

In currently marketed clindamycin phosphate vaginal cream 2% (Clindesse®), the most common adverse reactions, reported in ≥2% of patients and at a higher rate in the active treatment group than in the placebo group, were vaginosis fungal (14%), headache (7%), back pain (5%), constipation (2%), and urinary tract infection (2%) (Perrigo Specialty Pharmaceuticals, 2014).

Many oral antibiotics, including clindamycin, may cause overgrowth of dangerous bacteria in the large intestine (e.g. *Clostridium difficile*). This may cause mild diarrhea, or it may cause a life-threatening condition called colitis (inflammation of the large intestine). Clindamycin is more likely to cause this type of infection than many other antibiotics. Patients with Crohn's disease (regional enteritis), ulcerative colitis, or *C. difficile*-related diarrhea are not eligible for the study. Patients with other types of chronic enteritis or colitis should be discussed with the Medical Monitor prior to randomization.

Other known side effects of oral clindamycin treatment are listed below. This information is not based on treatment with 2% clindamycin vaginal gel, which would be expected to result in significantly lower systemic blood levels than those obtained with oral formulations.

- Nausea
- Vomiting
- Unpleasant or metallic taste in the mouth
- Joint pain
- Pain when swallowing
- Heartburn
- White patches in the mouth
- Thick, white vaginal discharge
- Burning, itching, and swelling of the vagina
- Peeling or blistering skin
- Rash
- Hives
- Itching
- Difficulty breathing or swallowing
- Hoarseness
- Swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs
- Yellowing of the skin or eyes
- Decreased urination

Potential benefits of DARE-BV1 in treatment of BV include its simplicity of use (a single application), its thermoreversible properties that should keep the product from leaking out and increase residence time, the well-established effectiveness of clindamycin in treating BV, and the infrequency of serious side effects associated with clindamycin use.

5.2.2 Assessment of Potential Risks and Benefits

Potential risks that may be associated with use of DARE-BV1 have been minimized in this study by the following:

- Establishing eligibility criteria that exclude patients with clinically significant conditions that would preclude DARE-BV1 use;
- Selecting Investigators with the proper level of training and experience in assessing and treating BV;
- Ensuring adequate monitoring is performed to identify any safety issues associated with the study procedure and patients; and
- Regularly reviewing reported serious adverse event (SAEs) and adverse events (AEs) throughout the study and taking appropriate medical measures to resolve the AEs.

The expected risk/benefit profile for DARE-BV1 is sufficient to perform this Phase 3 clinical study.

6 OBJECTIVES AND ENDPOINTS

6.1 PRIMARY OBJECTIVE AND ENDPOINT

The primary objective of the study is to assess the efficacy of DARE-BV1 for the treatment of BV in postmenarchal females.

The primary efficacy endpoint is the proportion of patients with Clinical Cure at the Test of Cure (TOC) visit (Day 21-30). Clinical Cure is defined as:

- Resolution of abnormal vaginal discharge associated with BV;
- Negative 10% potassium hydroxide (KOH) whiff test; and
- Clue cells < 20% of the total epithelial cells in the saline wet mount.

6.2 SECONDARY OBJECTIVES AND ENDPOINTS

The secondary efficacy endpoints of the study include assessment of Bacteriological Cure and Therapeutic Cure of BV in postmenarchal females. Secondary efficacy endpoints are:

- Proportion of patients with Bacteriological Cure at the TOC visit (Day 21-30). Bacteriological Cure is defined as a Nugent score < 4.
- Proportion of patients with Therapeutic Cure at the TOC visit (Day 21-30). Therapeutic Cure is 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 7-14).
- Proportion of patients with Bacteriological Cure (Nugent score <4) at the Interim Assessment visit (Day 7-14).
- Proportion of patients with Therapeutic Cure at the Interim Assessment visit (Day 7-14).

The secondary objective of the study is to assess the safety and acceptability of DARE-BV1. Assessments include:

- Clinical laboratory tests (chemistry, hematology, and urinalysis)
- OSOM® test for *Trichomonas vaginalis*

- Nucleic acid amplification tests (NAATs) for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
- Clinical and microscopic assessment for vulvovaginal candidiasis
- Vaginal culture for *Candida* species
- Review of treatment-emergent adverse events (TEAEs)
- Review of concomitant medications
- Acceptability Questionnaire

The PK assessment (PK subset only) is as follows:

- Pharmacokinetic blood draws to assess plasma clindamycin levels for Days 1-7
- Collect samples for vaginal clindamycin concentrations for Days 1-7

7 STUDY DESIGN

7.1 OVERALL DESIGN

This is a multicenter, randomized, double-blind, placebo-controlled study of DARE-BV1 clindamycin phosphate vaginal gel, 2% (daily [QD] × 1 day) compared to placebo vaginal gel (hydroxyethylcellulose [HEC] Universal Placebo Gel) (QD × 1 day) for the treatment of BV. Patients will be evaluated at 3 time points: a Day 1 Screening/Randomization visit, a Day 7-14 Interim Assessment visit, and a Day21-30 TOC visit (or a Day 21-30 Safety Follow-up phone call visit for patients who are prematurely discontinued). The total study duration will be up to approximately 1 month for a patient.

At the Screening/Randomization Visit (Day 1), past medical and obstetrical/gynecological/menstrual history, contraception and medically relevant sexual history, and lifetime BV history and number of episodes of BV in the preceding 12 months (along with treatment given) will be collected/evaluated. Signs and symptoms of BV will be evaluated, including color, odor and consistency of vaginal discharge, plus vulvovaginal itching and irritation will be assessed.

Additionally, the following samples/tests will be collected and performed: saline wet mount to assess clue cell percentage and other pertinent findings (e.g., trichomonads, white blood cells, other cellular and microbial elements), 10% KOH whiff test and KOH wet mount for yeast assessment; vaginal culture for *Candida* species; vaginal pH; slide preparation for centralized Gram stain for Nugent scoring, urine pregnancy test, NAATs for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, OSOM® test for *Trichomonas vaginalis,* blood sample for chemistry and hematology and urinalysis.

A major goal of the screening process is to confirm the presence of BV and to rule out the presence of other infectious and non-infectious causes of vulvovaginitis. Careful attention must therefore be paid to both the clinical assessment of the patient and to microscopic assessments (saline and KOH wet mount). However, the medical literature suggests that clinical and microscopic assessments are less than optimal at identifying patients with candidiasis (Schwebke, 2020; Lowe, 2009); therefore, a vaginal culture for *Candida* species will be obtained at baseline on each randomized patient, and used to determine if the patient will be included in the modified intent-to-treat (mITT) population. The NAAT testing for *N. gonorrhea* and *C. trachomatis* will be obtained for similar reasons, and rapid testing for *T. vaginalis* will be performed onsite to rule out *Trichomonas* prior to randomization.

In the event that there is any ambiguity in the patient's signs, symptoms, or microscopic assessments suggesting that the patient may have a mixed infection, then randomization and treatment should be delayed until the results of the yeast culture and/or NAATs are available (assuming the patient is able and willing to have treatment delayed for several more days). If the yeast culture (or NAAT) result is positive

(or if it is not feasible to delay treatment), then the patient should be screen-failed.

If, however, the patient's screening assessments support the diagnosis of BV only and the patient is randomized, but it is later learned that the *Candida* culture was positive at screening, the clinician should assess whether antifungal therapy is clinically warranted, or if the culture represents a subclinical condition that does not require medical treatment. An AE should be captured in the eCRF only if the patient requires treatment for signs/symptoms consistent with a yeast infection, i.e., a positive culture by itself does not constitute an AE.

Patients with positive NAAT results at screening for *C. trachomatis* or *N. gonorrheae* should be treated as indicated per the investigator's judgment, and an AE captured in the eCRF. In such cases, the AE eCRF question "Did this adverse event begin prior to using the study medication?" should be answered "Yes" to indicate that the AE onset was prior to dosing.

Patients should not be menstruating at the Screening/Randomization Visit, nor expected to begin menstruating during the 7 days after study drug administration; therefore, the optimal timing for the Day 1 visit should be carefully evaluated during pre-screening. If 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. For this reason (and others), split screening visits are allowed. Ideally the patient will return to the clinic as soon as possible after the end of her menses for completion of all assessments and randomization; however, a 14-day window is provided to accommodate this and other circumstances that could require a delay in randomization. Section 10.1.1 provides additional information regarding the assessments that must be completed on the day of randomization (Day 1), regardless of the reason for the delay.

At Visit 1 patients will also be provided with instructions for using a daily electronic diary (eDiary). The patient eDiary will be utilized to collect information regarding study drug administration, symptoms related to BV, relevant AEs and other pertinent information. Site staff will review the patient's eDiary responses with the patient at each study visit to ensure that all relevant information is documented in the electronic case report form (eCRF) (such as medication use and AEs since the previous visit).

Eligible patients will be randomly assigned via Interactive Response Technology (IRT) 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 will be applied intravaginally within 1 day of randomization.

The patients will return to clinic for Visit 2 on Day 7-14 for the Interim Assessment visit. A third and final visit will be conducted at Day 21-30 for Test of Cure (TOC). Similar to the requirement at randomization, patients should not be 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 the Visit 2 (Day 7-14) and Visit 3 (Day 21-30) visits, the Investigator will perform gynecological examinations and collect specimens for the following tests: saline wet mount to assess clue cell percentage, 10% KOH whiff test and wet mount microscopic yeast assessment, vaginal pH, preparation of slides for the 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 will be evaluated at each visit. Post-treatment blood chemistry and hematology assessments will be obtained at the TOC Visit (Visit 3, Day 21-30). If clinical symptoms (supported by microscopic findings) indicate active vulvovaginal candidiasis at Visit 2 or Visit 3, a vaginal yeast culture should be obtained. Repeat diagnostic testing for *N. gonorrhoeae, C. trachomatis or T. vaginalis* may also be obtained at any time if clinically warranted to determine the etiology of a change or worsening in vaginal discharge or other signs or symptoms. Any clinically significant conditions arising after randomization should be recorded as AEs.

Approximately 20 patients at selected sites (2-4 sites are anticipated) will participate in a PK study. The patients in this subset will apply the study drug at the study clinic during Visit 1 and will have blood draws for plasma clindamycin assessment taken at 0 hours (pre-dose) and then at 2, 4, 6, and 8 hours (±15 minutes) post-dose, as well as at 24, 48, 72, 96, 120, and 144 hours (±2 hours) post-dose (Days 2-7). In addition, samples for vaginal clindamycin concentrations will be collected on Days 1--7 (with the Day 1 sampling schedule starting pre-dose; no post-dose vaginal clindamycin samples will be collected on Day 1). For these patients, the assessments for the Interim Assessment (Day 7-14) visit may be done on the same day as the Day 7 PK draw.

Assessment and documentation of AEs and concomitant medications will occur at each visit. A review of patient-reported and Investigator-assessed local site reactions will occur at each visit after randomization and treatment. Patients' daily eDiary entries will be reviewed at each visit.

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 21-30). 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 21-30). If other BV treatment is prescribed at Visit 3, then the patient should either be followed by the study doctor (if the patient is regularly treated at their clinic), or referred back to their local health care 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 is for all patients to complete the study, regardless of whether additional BV treatment (or other antibacterial/antifungal therapy) is provided prior to completion of the final TOC visit/Visit 3. Patients who discontinue prematurely from the study for any reason will receive a Safety Follow-up phone call between Study Days 21-30 to assess the status of BV symptoms, AEs, and medication usage.

7.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A double-bind, placebo-controlled, randomized design is appropriate for investigating the efficacy, safety and acceptability of a vaginal antibiotic treatment for BV because this study design has been well-established in the published literature for evaluating BV treatment in a Phase 3 study. The study design is also consistent with the current U.S. Food and Drug Administration (FDA) draft guidance entitled "Bacterial Vaginosis: Developing Drugs for Treatment," dated August 2019.

7.3 JUSTIFICATION FOR DOSE

Use of one full applicator (5 g) of clindamycin phosphate vaginal gel, 2% (100 mg clindamycin) is justified based on published data for existing marketed vaginal clindamycin treatments for BV.

7.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last visit or procedure shown in the Schedule of Assessments in the trial globally.

7.5 STUDY DURATION

The study duration for each patient will be up to approximately 1 month: Visit 1 (Day 1) Screening/Randomization Visit including treatment; Visit 2 (Day 7-14) for interim assessment of efficacy

parameters and safety; and either the final Visit 3 (Day 21-30) assessment of efficacy and safety, or the Follow-up Safety Phone Visit (Day 21-30) for patients who discontinue prematurely from the study.

8 STUDY POPULATION

Patients with a clinical diagnosis of BV at the Screening/Randomization Visit who meet the following eligibility criteria may participate in the study.

8.1 INCLUSION CRITERIA

1. Patients must provide written informed consent prior to any study-related procedures being performed. Patients from 12 through 17 years old may participate where permitted by applicable local regulations and Institutional Review Board (IRB) 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 the saline wet mount
    c. Vaginal secretion pH of > 4.5
    d. A fishy odor of the vaginal discharge with the 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 throughout the first 7 days following treatment. Non-pregnant 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 21-30).
5. This trial will enroll pregnant women; however, non-pregnant 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 (IUDs), contraceptive implants under the skin, patches or injections, non-polyurethane 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 1 full cycle (e.g., 4 to 8 weeks) prior to study drug application. Injectable or implanted contraceptives (e.g., Depo-Provera, Nexplanon, or hormonal IUD) must have been injected/inserted at least 7 days prior to study drug application.

    Patients who are not of childbearing potential will not need a urine pregnancy test prior to randomization or at subsequent visits. The patient is considered to be of non-child bearing potential if one of the following is 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. Non-surgical permanent sterilization procedure performed at least 3 months prior to study drug application.

Patients must be willing to refrain from the use of all intra-vaginal products (e.g., douches, feminine deodorant sprays, condoms, spermicides, vaginal moisturizers or lubricants, tampons, vaginal birth control rings [e.g., NuvaRing®], and diaphragms) through the first 7 days at a minimum, and ideally through Visit 3 (Day 21-30) or Study Exit/Early Discontinuation.

8.2 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 (HPV), *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 *C. 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 HPV 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.

8.3 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical trial but are not randomized to receive treatment. Screen failures may be re-screened in cases where the unmet selection criteria have been resolved after previous screen failure. A new Informed Consent Form (ICF) will be needed for re-screened patients if more than 30 days have passed since informed consent was obtained. Re-screened patients who are re-screened past the 30-day window and are re-consented will be assigned a new patient number. Randomized patients prematurely withdrawn from the study will not be replaced.

8.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited to this study by the participating study physicians. Advertising will be allowed in accordance with applicable regulations and as approved by the Sponsor or designee and the IRB.

9 STUDY INTERVENTION

9.1 STUDY INTERVENTION ADMINISTRATION

9.1.1 Study Intervention Description

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

Reference Therapy, Dose and Mode of Administration: Placebo vaginal gel (HEC Universal Placebo Gel) will also be supplied in matching tubes with accompanying applicators, as above. One full applicator of placebo vaginal gel (5 g) will be applied intravaginally as a single dose.

Additional details regarding clinical trial material will be provided in the pharmacy manual.

9.1.2 Dosing and Administration

One full applicator (5 g) of clindamycin phosphate vaginal gel, 2% (100 mg clindamycin) or placebo gel will be applied intravaginally as a single dose within 1 day of randomization.

9.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

9.2.1 Acquisition and Accountability

Receipt, use and return of the study drug will be documented in an accountability log in each site's regulatory file. The log should specify lot/batch number and dates of supply and return. Study drug will not be distributed to the participating center until all agreements between the Principal Investigator and Sponsor are finalized and IRB approvals have been obtained. Distributed study drug will be used only for this study, in accordance with this protocol and instructions for use.

At the end of the study, the monitor will review final accountability of all clinical supplies. Used study drug destruction/disposal will occur on-site following site-specific destruction standard operating procedures in accordance with instructions provided by the Sponsor or designee. If destruction services are not available on-site, unused study drug will be returned to the packaging and labeling vendor for destruction services. Guidance for remaining unused study product return or disposal will be provided by the Sponsor at the end of the study.

9.2.2 Formulation, Appearance, Packaging, and Labeling

The study drug will be supplied with appropriate packaging and labeling in accordance with International Council for Harmonisation (ICH) E6 (R2) Section 5.13 and 21 Code of Federal Regulations (CFR) 312.6. Details regarding study drug packaging, labeling, and use instructions will be provided in the study reference manual.

9.2.3 Product Storage and Stability

The study drug should be stored at room temperature between 15°C (59°F) and 30°C (86°F), and in a secured space at each site. All clinical supplies should only be handled by authorized personnel according to the delegation log in the site regulatory file.

9.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

9.3.1 Randomization

Randomization will occur after a patient's eligibility has been confirmed. Patients will be assigned a unique patient identification number by the site at screening. Following completion of the screening procedures, eligible patients will be randomized in a blinded manner via the validated, access controlled, IRT system. Stratification factors in the randomization are: PK subset (Yes/No), site, and race (African-American/Black versus all others). Patients will be randomized to 1 of 2 treatment groups (DARE-BV1 [clindamycin phosphate vaginal gel, 2%] or placebo vaginal gel) in a 2:1 ratio, with approximately 188 patients be randomized to DARE-BV1, and 94 patients randomized to placebo vaginal gel.

Randomization will be requested by adequately trained and delegated site staff with appropriate user access to the IRT system. Unique patient randomization numbers and treatment allocations will be provided within the IRT system and will be generated from the randomization scheme. A randomization number will be automatically provided by the IRT system and confirmed by email, ensuring concealment of treatment allocation.

9.3.2 Blinding

This is a double-blind study. The Principal Investigator and other site staff will be blinded to study treatment throughout the conduct of the study. Treatment randomization information will be kept confidential and will not be released to the blinded Investigator or blinded Investigator site personnel until the study database has been locked or the Investigator requests unblinding for safety reasons.

At the initiation of the study, the site will be instructed on procedures for breaking the blind for safety reasons. The study blind should be maintained whenever possible to avoid bias. Active study drug and placebo reference therapy will be packaged in matching tubes with accompanying applicators.

If the treatment assignment must be revealed for the safety of the patient or to treat an AE, the Investigator should contact the Medical Monitor or designee. A decision to break the blind should be reached by the Medical Monitor or designee and the Investigator.

The Investigator or designee may break the blind independent of the Medical Monitor only if it is considered an emergency by the Investigator. If this occurs, the Medical Monitor and the Sponsor must be notified within 24 hours of breaking the blind.

The event requiring breaking the blind must be documented and reported appropriately, including the date the blind was broken.

9.4 STUDY INTERVENTION COMPLIANCE

Participants will return their study drug tube and applicator following use. Study drug compliance will be verified through confirmation of the weight of the study drug tube prior to dispensation and upon return to the study site. Additional dosing information will be captured in real-time via patient reported eDiary

entries to ensure application procedures were properly followed. Finally, compliance information will be recorded for each patient on a study-specific drug accountability log.

Instances of significant over- or under-dosing are considered protocol deviations but will not be automatically recorded as AEs. Any undesirable medical occurrence resulting from significant over- or under-dosing is an AE and should be recorded and reported on the AE eCRF. The Investigator should record the event in the source document and should monitor the subject.

9.5 ELECTRONIC DIARY

Patients will be instructed on how to use their daily eDiary at Visit 1. Site staff will review eDiary entries with patients at each study visit and ensure that any relevant information pertaining to new medications or AEs has been appropriately captured in the eCRF.

9.6 CONCOMITANT THERAPY

Concomitant medications include any medication or health product (any prescription medications or over-the-counter preparations) taken from the time the patient signs the informed consent documents until study exit and must be reported appropriately on the eCRF. Information on prior medications taken within 30 days of consent should be collected (including supplements and herbal remedies in addition to prescription and over-the-counter medications).

Recording of all concomitant treatments will occur on the patient's source and eCRF, including the name of the drug, dose, start and stop dates, and reason for use, from the time the ICF is signed through completion or discontinuation from the trial. Any other investigational product must have been stopped at least 30 days before the start of screening for this trial. Other medications for the treatment of inter-current medical conditions will be permitted and recorded as detailed above unless identified as prohibited medications.

Patients should not have received antifungal or antibacterial therapy (systemic or intravaginal) during the 14 days prior to the Screening/Randomization Visit (Visit 1). Patients on suppressive antiviral therapy for herpes simplex infections are considered eligible for the study provided they have remained asymptomatic for at least 6 months prior to screening (as per Exclusion Criterion #1) and antiviral therapy is expected to continue in a stable fashion for the duration of the study. Patients receiving antiviral therapy for other indications at the time of screening should be assessed on a case-by-case basis and discussed with the Medical Monitor prior to randomization. Oral probiotics are permitted, provided usage has been stable for at least 1 month prior to randomization and is intended to remain stable during the patient's study participation.

Patients enrolled and treated in this study who have lack of relief of BV symptoms at or prior to Visit 3 and are treated with other BV therapy should not be discontinued from the study. The same is generally true for patients requiring any other antimicrobial therapy during their study participation. Patients who satisfy all eligibility criteria based on clinical and microscopic assessments at screening, but then, after randomization and dosing, are discovered to be positive for Chlamydia (CT), gonorrhea (NG), or Candida based on their screening NAATs or Candida culture, should be encouraged to complete the study; i.e., they should not be discontinued solely due to positive screening laboratory results--unless there are reasons why it is not in the patient's best interest to continue in the study. The goal is for all patients to complete the study whenever feasible and appropriate; therefore, any patient requiring antifungal, antibacterial (whether for BV or an unrelated indication), or antiviral therapy should be assessed on a case-by-case basis, and if in doubt, discussed with the Medical Monitor, to determine if/when it is not appropriate for the patient to continue in the study.

9.7 PATIENT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Each patient will be informed of her right to withdraw from the study at any time and for any reason. A patient may be discontinued from the study at any time if the patient, the Investigator, or the Sponsor feels that it is not in the patient's best interest to continue in the study.

Patients who sign the ICF and agree to participate in the study, but do not meet eligibility criteria, will be considered screen failures.

Following enrollment, patients may be discontinued from the study for the following reasons:

- Lack of compliance (i.e., failure to follow protocol requirements that is judged severe enough by the Investigator to significantly affect study outcomes)
- Any AE or intercurrent illness that would jeopardize the patient's health or the interpretation of the results of the study
- Lost to follow-up
- Patient withdrawal of consent
- Treatment failure
- Retrospective discovery of an entry criterion violation
- Pre-existing condition or abnormality, including abnormal laboratory or microbiological result obtained at screening
- Other (e.g., sponsor decision, pregnancy during the study, logistical issues related to Covid-19, etc.)

Prior to discontinuing a patient from the study, the site should contact Daré or designee. The reason for discontinuation must be recorded on the appropriate section of the patient's eCRF and Early Discontinuation procedures should be performed.

9.8 LOST TO FOLLOW-UP

A patient cannot be considered withdrawn due to becoming lost to follow-up (LTFU) until the research site performs and documents at least 3 attempts to contact her. Documentation must include at least 1 letter sent via a method that allows a "return receipt," e.g., certified mail, to be requested with instructions provided to the patient to contact the research site. Every reasonable effort must be made to follow up with patients who discontinue with study drug-related AEs in order to determine the final outcome.

Patients designated as LTFU who later resume contact with the site should be requested to come in for an unscheduled visit to complete early discontinuation procedures. Documentation should include the period of time they were out of contact with the site (after last contact). If the Investigator anticipates future problems with follow up, then the patient should be withdrawn from the study.

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 STUDY VISITS

The study will include 3 scheduled in-clinic visits for all patients, plus a follow-up phone call for patients who discontinue prematurely:

- Visit 1: Screening/Randomization for all patients

- Visit 2 (Days 7-14): Interim Assessment for all patients
- Visit 3 (Days 21-30): TOC for all patients
- Safety Follow-up Phone Visit (Days 21-30) for all prematurely discontinued patients

For patients in the PK subset only, there will be additional blood draws and vaginal clindamycin concentration collections at the Screening/Randomization Visit (Day 1) as well as 5 additional visits between Visit 1 and Visit 2 (Visits PK1-PK5 on Days 2 through 6). The assessments for the Interim Assessment Visit (Day 7-14) may be done on the same day as the Day 7 PK draw.

Refer to the Schedule of Assessments for the study (Table 1) and for the PK subset (Table 2) as well as the by-visit descriptions below for additional details.

10.1.1 Visit 1: (Day 1) Screening/Randomization

All Visit 1 (Screening/Randomization) procedures should be completed on the same day when feasible. If it is not feasible to complete all assessments on the same day, or if the patient's menstrual cycle requires a delay in randomization, then confirmation of eligibility must be repeated at the time of randomization. The specific assessments that must be performed on the day of randomization are identified below; the Investigator may use clinical judgment to decide whether other assessments should also be repeated. If randomization does not occur on same day as the initial screening visit, the patient should return no later than 14 days from start of screening (i.e., the signing of the ICF) for randomization.

During Visit 1, the following procedures should be performed. All assessments must be completed prior to randomization; however, if randomization must be delayed and a split screening visit is utilized, then the asterisked and italicized assessments below must then be completed (or repeated) on the day of randomization.

- Written informed consent administration
- Demographics
- Collection of medical, gynecological, contraceptive, menstrual, and relevant sexual history
- Height
- *Weight**
- *Vital signs**
- *Prior and concomitant medications assessment**
- *Adverse events assessment**
- *Urine pregnancy test**
- *In clinic urine dipstick**
- Urinalysis
- Hematology/chemistry
- Complete physical examination
- *Pelvic examination**
- *Amsel's criteria assessments*:*
    - *Vaginal discharge evaluation**
    - *KOH whiff test**
    - *Clue cells (wet mount)**
    - *Vaginal secretion pH**
- *Evaluate signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation**

- *Assessment of patient-reported and Investigator-assessed local site reactions* (i.e., patient-reported burning/stinging, vulvovaginal pain or pruritus, and Investigator-assessed vulvovaginal erythema, edema, petechiae or erosions/ulcers).*
- *Utilizing a swab of the vaginal pool, prepare a KOH wet mount for microscopic yeast assessment (this may be performed on the same sample used for the KOH whiff test)**
- *Collect swab for vaginal Candida culture**
- *Swab the lateral vaginal wall and prepare slides for centralized Nugent scoring as outlined in the study procedures manual**
- *Perform OSOM® test for Trichomonas vaginalis**
- *Collect swabs for Chlamydia trachomatis and Neisseria gonorrhoeae NAATs**
- *Review eligibility criteria**
- *Randomize patient (if patient meets all eligibility requirements)**
- *Review instructions and provide training on use of eDiary**
- *Dispense study drug and provide instructions to randomized patients. Under all circumstances study drug should be applied within 1 day of randomization.**
- ***PK subset patients only**: PK blood draws for plasma clindamycin assessment taken at 0 hours (pre-dose) and then at 2, 4, 6, and 8 hours (±15 minutes) post-dose. A baseline swab sample for vaginal clindamycin concentration assessment will be taken at Visit 1/Day 1 at 0 hours (pre-dose) only; vaginal clindamycin samples will **not** be taken at post-dose timepoints during Visit 1/Day 1.**

10.1.2 Visits PK1-PK5 (Days 2, 3, 4, 5, and 6): Pharmacokinetic Draw Visits (for Pharmacokinetic Subset Only)

During Visits PK1-PK5 for patients **in the PK subset only**:

- PK blood draws for clindamycin plasma level assessment and swab samples for vaginal clindamycin concentration assessment will be done at:
  - Visit PK1 (Day 2, 24 hours [±2 hour] post-dose)
  - Visit PK2 (Day 3, 48 hours [±2 hour] post-dose)
  - Visit PK3 (Day 4, 72 hours [±2 hour] post-dose)
  - Visit PK4 (Day 5, 96 hours [±2 hour] post-dose)
  - Visit PK5 (Day 6, 120 hours [±2 hour] post-dose)
- Concomitant medications assessment
- Adverse events assessment

10.1.3 Visit 2 (Days 7-14): Interim Assessment

During Visit 2 (Days 7-14)/Interim Assessment, the following procedures should be performed:

- Vital signs
- Record treatment application date
- Concomitant medications assessment
- Adverse events assessment
- Urine pregnancy test
- In clinic urine dipstick
- Pelvic examination
- Assessment of patient-reported and Investigator-assessed local site reactions
- Amsel's criteria assessments:

  - Vaginal discharge evaluation
  - KOH whiff test
  - Clue cells (wet mount)
  - Vaginal secretion pH
- Evaluate signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation
- Swab the vaginal pool and prepare KOH wet mount for microscopic yeast assessment (this may be performed on the same sample used for the KOH whiff test)
- Swab the lateral vaginal wall and prepare slides for centralized Nugent scoring as outlined in the study procedures manual
- Collect used/unused study drug and perform compliance assessment by weighing the returned used tube; record weight in the eCRF
- Review eDiary
- Administer Acceptability Questionnaire
- ***PK subset patients only:*** *PK blood draw should be done on Day 7 (144 hours [±2 hour] post-dose). Also, for the PK subset only, collect samples for vaginal clindamycin concentration assessment. The other assessments for the Day 7 – 14 visit may be done on the same day as the Day 7 PK draw*

10.1.4 Visit 3 (Days 21-30): Test of Cure (TOC)

During Visit 3 (Days 21-30)/TOC, the following procedures should be performed:

- Vital signs
- Concomitant medications assessment
- Adverse events assessment
- Urine pregnancy test
- In clinic urine dipstick
- Urinalysis
- Hematology/chemistry
- Directed physical examination
- Pelvic examination
- Assessment of patient-reported and Investigator-assessed local site reactions
- Amsel's criteria assessments:
  - Vaginal discharge evaluation
  - KOH whiff test
  - Clue cells (wet mount)
  - Vaginal secretion pH
- Evaluate signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation
- Swab the vaginal pool and prepare KOH wet mount for microscopic yeast assessment (this may be performed on the same sample used for the KOH whiff test)
- Swab the lateral vaginal wall and prepare slides for centralized Nugent scoring as outlined in the study procedures manual
- Review eDiary
- Administer Acceptability Questionnaire

10.1.5 Early Discontinuation Visit

At Early Discontinuation visits, the following procedures should be performed:

- Vital signs
- Concomitant medications assessment
- Adverse events assessment
- Urine pregnancy test
- In clinic urine dipstick
- Urinalysis
- Hematology/chemistry
- Directed physical examination
- Pelvic examination
- Assessment of patient-reported and Investigator-assessed local site reactions
- Amsel's criteria assessments:
    - Vaginal discharge evaluation
    - KOH whiff test
    - Clue cells (wet mount)
    - Vaginal secretion pH
- Evaluate signs and symptoms of BV, including color, odor, and consistency of vaginal discharge, vulvovaginal itching, and irritation
- Swab the vaginal pool and prepare KOH wet mount for microscopic yeast assessment (this may be performed on the same sample used for the KOH whiff test)
- Swab the lateral vaginal wall and prepare slides for centralized Nugent scoring as outlined in the study procedures manual
- Collect PK sample if patient was enrolled in that subset and discontinuation was within the first 7 days
- Review eDiary
- Administer Acceptability Questionnaire

10.1.6 Safety Follow-up Phone Call

Patients who discontinue early from the study will receive a follow-up phone call from the site staff between Study Day 21-30. Patients will be asked questions regarding AEs, concomitant medications and the status of their BV symptoms.

10.1.7 Unscheduled Visits

Unscheduled visits are allowed at the discretion of the Investigator for safety assessments or administrative reasons. During unscheduled visits, the Investigator will perform any study assessments or other safety assessments as necessary to provide appropriate treatment.

10.2 EFFICACY ASSESSMENTS

The primary efficacy endpoint (Clinical Cure at the TOC visit [Day 21-30]) is the resolution of the following 3 BV signs included in Amsel's criteria (Amsel, 1983): abnormal vaginal discharge associated with BV as determined by the Investigator, positive KOH whiff test, and the presence of clue cells at >20% of the total epithelial cells on microscopic examination of the saline wet mount.

The supportive secondary efficacy endpoints are the Bacteriological Cure and the Therapeutic Cure. The bacteriological cure is defined as Nugent's score <4 (via Gram stain performed by a central laboratory). A Nugent score ≥4 is considered abnormal and represents an imbalance in vaginal flora that permits BV to manifest (Nugent, 1991). Patients who are responders are expected to achieve a normal Nugent score (i.e., 0 through 3) following treatment.

Therapeutic cure is defined as having achieved both Clinical Cure (i.e., resolution of abnormal discharge associated with BV, negative whiff test and <20% clue cells on wet mount) and Bacteriological Cure (i.e., Nugent score of <4).

10.3 SAFETY AND OTHER ASSESSMENTS

10.3.1 Medical, Gynecological, Contraceptive, and Relevant Sexual History

A complete medical, gynecological, contraceptive, and relevant sexual history will be collected at Visit 1, including prior and concomitant illnesses. The recorded information will include: acute and chronic history of medical and gynecological conditions (including history of BV), smoking, illicit drug and alcohol use history, menstrual cycle history (start date of last menstrual cycle and expected timing of next menses will be collected), medically relevant sexual history including history of sexually-transmitted infections (STIs), current sexual activity, previous/current contraceptive use, and pregnancy history.

10.3.2 Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded at Visit 1.

10.3.3 Vital Signs, Height, and Weight

Vital sign measurements will be taken at each visit and include sitting (after 5 to 10 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and oral temperature per standard of care. Height and weight will be measured only at Visit 1.

10.3.4 Urine Pregnancy Test

Pregnancy testing via urine human chorionic gonadotropin (hCG) testing will be performed for each patient, unless the patient is not of childbearing potential as defined in Inclusion Criterion #5, at each visit (serum hCG testing will be done only if deemed necessary by the Investigator). Additional pregnancy testing may also be performed if there is any suspicion or clinical concern that a woman might be pregnant at any time during the study.

10.3.5 Urinalysis

Onsite dipstick urinalysis will be performed at Visit 1 (Screening), Visit 2 (Interim Assessment), Visit 3 (TOC), and at the Early Discontinuation Visit as specified in the Schedule of Assessments (Table 1 and Table 2 [for PK subset]). In addition, a full urinalysis will be performed by the central laboratory for Visit 1 (Screening), Visit 3 (TOC), and at the Early Discontinuation visit. If an abnormal laboratory result from the screening assessment is judged by the Investigator as being clinically significant but not exclusionary, it should be reported as medical history. If clinical symptoms or urinalysis results at screening suggest that the patient may have a urinary tract infection that could require antibiotic therapy, then the patient should be screen failed and referred for further evaluation.

10.3.6 Hematology/Chemistry

Samples for hematology and clinical chemistry assessments will be collected at Visit 1 (Screening), Visit 3 (TOC), and the Early Discontinuation visit as specified in the Schedule of Assessments (Table 1 and Table 2 [for PK subset]). If an abnormal laboratory result from the screening assessment is judged by the Investigator to be clinically significant, it should be reported as medical history.

10.3.7 Physical Examination

A complete physical examination should be performed at Visit 1. A directed physical exam should be performed at Visit 3 and at the Early Discontinuation visit (if applicable), in accordance with the Investigator's judgment. Clinically significant physical examination findings should be reported as medical history or AEs, as appropriate. Rectal and breast examinations are not required for either the complete or directed physical exams.

10.3.8 Pelvic Examination

A pelvic examination will be performed at each visit and will include a vaginal wall inspection as well as an examination of the cervix, and confirmation that all findings are consistent with BV, versus *Candidiasis* or other causes of the patient's vaginal signs or symptoms. Any observed abnormalities will be assessed and documented in the source document and eCRF.

10.3.9 Specimen Collection

At Screening, swabs will be collected and submitted for the *Candida* culture, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* NAATs, and the OSOM® test for *Trichomonas vaginalis* (which will be performed onsite). A swab of the vaginal pool should be utilized to perform a microscopic wet mount evaluation for clue cells (as part of Amsel's criteria) as well as other elements (e.g., white blood cells, trichomonads, yeast, bacteria, etc.). Vaginal samples will also be used for microscopic KOH wet mount evaluations to assess the presence of *Candida* species.

A swab of the lateral vaginal wall should be utilized for the slides to be submitted for centralized Gram staining for Nugent scoring. Instructions for the sampling for all procedures, including vaginal *Candida* cultures, preparation of slides for Nugent scoring, and NAAT and OSOM® testing, will be included in the laboratory manual and/or other study documents.

10.3.10 Prior and Concomitant Medications

All medications taken during the 30 days prior to signing the ICF or used during the patient's study participation will be recorded at each visit and documented in the eCRF.

10.3.11 Adverse Events

Assessment of AEs will be completed at all visits. Any untoward events reported by the patient or observed by the study staff during or following treatment are to be recorded as AEs. (Events that occur after signing the ICF but before treatment with study drug are to be recorded and reported either as medical history or pre-treatment AEs, as appropriate.) Refer to Section 10.4 for details regarding definitions, documentation, and reports of AEs and SAEs.

10.3.12 Local Site Reactions

At each visit the Investigator or designee will perform a vulvar-vaginal examination to assess the treatment area and rate the following on a scale of 0 = absent, 1 = mild (slight, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense):

- Erythema
- Petechiae
- Erosion/ulceration
- Edema

The patient will be queried by the Investigator or designee for presence of the following and, if present, the patient will be asked to rate as described above:

- Burning/stinging
- Pain
- Pruritus (itching)

A separate eCRF will be designed to identify, track and characterize all local site reactions; therefore, vulvovaginal symptoms should be reported as TEAEs only if they are of a magnitude suggesting a clinically significant worsening compared to the patient's baseline condition, or they require medical intervention.

10.3.13 Acceptability Assessment

Patients will provide responses to questions of product acceptability, including the patient's experience with changes in odor and discharge. Additionally, information will be collected to understand the patient's experience with the study drug itself, e.g., ease of application, messiness or lack thereof, etc.

10.3.14 Pharmacokinetics and Vaginal Clindamycin Assessments

For patients that have agreed and consented to participate in the PK subset group, PK blood draws will be done at 0 hours (pre-dose) and then at 2, 4, 6, and 8 hours (±15 minutes) post-dose (Day 1), as well as at 24, 48, 72, 96, 120, and 144 hours (±2 hours) post-dose (Days 2-7).

Also in the PK subset, samples will be collected for assessment of vaginal clindamycin concentrations at baseline (pre-dose only on Day 1; i.e., vaginal clindamycin samples will **not** be collected at post-dose time points on Day 1) as well as post-treatment on Days 2-7.

10.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.4.1 Definition of Adverse Events

An AE in a study of an investigational drug is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) associated with the use of a drug in humans, whether or not considered related to the drug.

10.4.2 Definition of Serious Adverse Events

An event is considered an SAE if, in the view of either the Investigator or Sponsor, it meets the criteria as outlined in 21 CFR 312.32 (a) as per the following:

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.4.3 Classification of an Adverse Event

10.4.3.1 Severity of Event

The Investigator is responsible for assessing the severity of each AE using the following definitions:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
- Severe: Symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 10.4.2. An AE of severe intensity may not be considered serious.

If there is a change in severity of an AE, it must be recorded as a separate event.

10.4.3.2 Relationship to Study Intervention

An Investigator who is qualified in medicine (e.g., MD, NP, DO) must make the determination of relationship to the study drug for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. For each AE, the assessment of relatedness should be made using the following scale:

- Unrelated: Onset of the AE had no reasonable temporal relationship to administration of the study product or a causal relationship to administration of the study product is biologically implausible or the event is attributed to an alternative etiology.
- Possibly Related: Onset of the AE has a reasonable temporal relationship to study product administration and a causal relationship is not biologically implausible.
- Probably Related: Onset of the AE has a strong temporal relationship to administration of the study product that cannot be explained by the patient's clinical state and a causal relationship is not biologically implausible.
- Definitely Related: Onset of the AE shows a distinct temporal relationship to administration of the study product that cannot be explained by the patient's clinical state or other factors or the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.

If the relationship between the AE/SAE and the investigational product is determined to be "possible," "probable," or "definite" the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

10.4.4 Time Period and Frequency for Event Assessment and Follow-up

All AEs must be recorded in detail in the source documentation, reported on the appropriate page in the eCRF, and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, until the patient is considered to be stable, or when a plan for appropriate follow-up has been approved by the Medical Monitor.

10.4.5 Adverse Event Reporting

All AEs reported or observed during the study shall be recorded in the source documentation and reported on the AE page in the eCRF. Information to be collected includes the patient's study ID number, age, site, concomitant drug treatment, and dose (if available), event term, time of onset, Investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, outcome, and period of study at onset (at screening, during treatment, or at follow-up). Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concomitant medications, or progression of disease states must also be reported. All AEs shall be followed-up until adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) shall be used to code all AEs.

Any medical condition that is present at the time the patient is screened but does not deteriorate after treatment shall not be reported as an AE. However, if it deteriorates at any time during the study, it shall be recorded as an AE.

10.4.6 Serious Adverse Event Reporting

Any AE that meets SAE criteria must be reported to the Sponsor or designee immediately (within 24 hours) after the time site personnel first learn about the event.

The study clinician shall immediately report to the Sponsor or designee any SAE, whether or not considered study intervention related, including those listed in the protocol or Investigator's Brochure, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All SAEs shall be followed-up until satisfactory resolution or until the site Investigator deems the event to be chronic or the patient is stable. Other supporting documentation of the event may be requested by the study Sponsor or designee and shall be provided as soon as possible.

The study Sponsor or designee shall be responsible for notifying the U.S. FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's or designee's initial receipt of the information. In addition, the Sponsor or designee must notify the U.S. FDA and all participating Investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor or designee determines that the information qualifies for reporting.

The Sponsor or designee and all applicable Investigators are also responsible for reporting new safety information to regulatory agencies as required in accordance with applicable local laws and regulations.

10.4.7 Reporting of New Information to Patients

Study patients will be notified in a timely manner of any new safety information that may affect their consent to participate in the study.

10.4.8 Reporting of Pregnancy

All pregnancies that occur while a patient is participating in the study will be reported immediately (within 24 hours) to the Sponsor or designee and monitored until outcome. Information from medical records will also be collected on pregnancy outcome data including maternal or fetal complications, spontaneous or elective abortions, ectopic pregnancies, stillbirths, and live preterm and full-term births. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of 8 weeks. Any congenital anomaly/birth defect in a child born to a patient exposed to the test article(s) should be recorded as a SAE and details appropriately documented. Spontaneous abortions will be considered non-serious unless associated with consequences that meet seriousness criteria.

Patients who are pregnant at the time of study enrollment will also be followed until delivery/termination of pregnancy and their offspring followed for a minimum of 8 weeks. The same information collected for patients who become pregnant during the study will be collected on patients who enter the study while pregnant.

11 STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan (SAP) will be finalized before the treatment assignments for all patients are unblinded and prior to locking the database to expand upon the statistical methods presented below.

11.1 STATISTICAL HYPOTHESES

The hypothesis test for the primary endpoint will be done to determine if DARE-BV1 is superior to placebo for Clinical Cure at the TOC visit (Visit 3; Day 21-30).

11.2 RANDOMIZATION AND STRATIFICATION

Randomization will be done in a 2:1 ratio (DARE- BV1 [clindamycin phosphate vaginal gel. 2%]: placebo vaginal gel). The randomization schedule will be generated using SAS® version 9.4 or higher. The randomization schedule will be stratified by site and race (African-American/Black versus all others).

11.3 SAMPLE SIZE DETERMINATION

The sample size calculations were performed using SAS® version 9.4 for the 2-group chi-square test. It is expected that this test will provide approximately the same power as the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center and race. A sample size of 188 DARE-BV1 versus 94 placebo patients (282 patients total) will have 90% power to detect a statistically significant difference at a significance level of 0.05 (2-tailed) under the assumption the clinical cure rates will be 55% and 30% for DARE-BV1 and placebo, respectively. This sample size assumes 35% of randomized patients will not be in the mITT population.

11.4 POPULATIONS FOR ANALYSES

Intent-to-Treat (ITT): All randomized patients

Safety: All ITT population patients who applied study drug

PK Subset (PKS): All Safety population patients who are enrolled into the PK subset

Modified Intent-to-Treat (mITT): All Safety population patients except those excluded due to demonstrating 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 are determined to have a baseline Nugent score of < 7. If the Nugent score at baseline is missing, then the patient is excluded from the mITT population.

Per-Protocol (PP): The PP population will include patients from the mITT population who either receive other BV therapy during the study for any reason, or meet the following criteria:

- Meet all 4 Amsel's criteria at screening
- Apply study drug within 1 day of randomization
- Do not use a prohibited medication prior to the Day 21-30 visit
- Attended the Day 21-30 visit
- Have no other major protocol violations that impacted the primary or secondary endpoints.

For the mITT and PP populations, if the patient receives other BV therapy for any reason, the patient will be included in the analysis as a treatment failure for all visits on or after receipt of the other therapy. Patients will 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 will 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.

11.5 STATISTICAL ANALYSES

11.5.1 General Approach

All statistical processing will be performed using SAS®, Version 9.4, or later. Continuous variables will be summarized with number of patients (N), mean, median, standard deviation (SD), minimum (Min), and maximum (Max). Categorical variables will be summarized with frequency counts and percentages.

All efficacy analyses will be conducted using a 2-sided test at an alpha level of 0.05. The primary efficacy analyses will be conducted on the mITT population. Additionally, efficacy analyses will be performed on the PP population and will be considered supportive. Safety analyses will be performed on the Safety population. Patients will be analyzed according to the treatment to which they were randomized for ITT and mITT analyses, regardless of actual treatment received. For all other analysis populations, patients will be analyzed according to the treatment they received.

11.5.2 Analysis of the Primary Efficacy Endpoint

All efficacy endpoints will be summarized for each treatment group using descriptive statistics, including 95% confidence intervals (within treatment group), as appropriate.

The primary efficacy analysis of Clinical Cure at Day 21-30 will be analyzed for the mITT population with a CMH test stratified by study center and race (African-American/Black versus all others). The

method for handling of patients in the mITT analysis without a Clinical Cure result at Day 21-30 will be included in the final SAP.

Patients who receive other BV treatment(s) for any reason will be included in the analysis as treatment failures for all visits on or after receipt of the other therapy(ies).

11.5.3 Analysis of the Secondary Endpoints

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

1. Proportion of patients in the mITT population with Bacteriological Cure at the TOC visit (Day 21-30). Bacteriological Cure is defined as a Nugent score < 4.
2. Proportion of mITT patients with Therapeutic Cure at the TOC visit (Day 21-30). Therapeutic Cure is defined as both a Clinical Cure and Bacteriological Cure (Nugent Score < 4).
3. Proportion of mITT patients with Clinical Cure at the Interim Assessment visit (Day 7-14).
4. Proportion of mITT patients with Bacteriological Cure (Nugent score < 4) at the Interim Assessment visit (Day 7-14).
5. Proportion of mITT patients with Therapeutic Cure at the Interim Assessment visit (Day 7-14).

Analysis of the secondary endpoints will follow the same method as the analysis of the primary endpoint, including patients being included in the analysis as treatment failures if other BV treatments were received (i.e., treatment failure status will be applied to all visits on or after receipt of the other BV treatment).

The PP population will be used to perform sensitivity analyses of the above primary and secondary efficacy analyses. Patients in the PP population without a Clinical Cure result at Day 21-30 will be excluded from the PP analyses.

11.5.4 Safety Analyses

Descriptions of AEs will 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 TEAEs occurring during the study will be recorded and classified on the basis of MedDRA terminology. Treatment-emergent AEs are those AEs with an onset at the time of or after the application of study drug. All reported TEAEs will be summarized by treatment group, system organ class and preferred term. Adverse event summaries will include severity, relationship to study drug, and seriousness. When summarizing events by causality and severity, each patient will 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 an SAE or who prematurely discontinued from the study due to an AE will be provided.

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

Local site reactions will be summarized at each visit.

Changes from baseline to each visit will be summarized for other safety parameters (e.g., vital signs, pelvic examination).

11.5.5 Pharmacokinetic Analysis

The following PK parameters will be summarized for the PKS population to assess plasma and vaginal clindamycin concentration levels for Days 1-7:

- minimum concentration (C_{min})
- maximum concentration (C_{max})
- area under the curve (AUC_{0-t}), where t is the last time-point with measurable concentration)
- time to maximum concentration (T_{max})
- elimination half-life ($t_{1/2}$)

Descriptive summaries of plasma clindamycin levels will be presented for each timepoint.

11.5.6 Baseline Descriptive Statistics

Demographic data and other baseline characteristics including medical and medication history will be summarized as appropriate.

11.5.7 Product Acceptability

Patients will provide responses to questions of product acceptability, including the patient's experience with changes in odor and discharge. Additionally, information will be collected to understand the patient's experience with the study drug itself, e.g., ease of application, messiness or lack thereof, etc. The results will be summarized for the Safety population.

11.5.8 Planned Interim Analyses

No interim analyses are planned.

11.5.9 Sub-group Analyses

Any sub-group analyses will be defined in the SAP that will be finalized prior to database lock.

11.5.10 Tabulation of Individual Patient Data

By-patient data listings will be provided to support all tabulated output.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1.1 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Guideline for Good Clinical Practice (GCP) E6 (R2), and all applicable regulations.

12.1.2 Institutional Review Board

Federal (U.S.) regulations, applicable laws and regulations in Canada and Europe, and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies.

Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH Harmonised Tripartite Guideline E6 (R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study as specified by the IRB. The Investigator must promptly supply the Sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

12.1.3 Informed Consent Process

A written ICF in compliance with ICH Guideline for GCP E6 (R2) and U.S. Title 21 CFR Part 50 will be obtained from each patient before entering the study. No study-related procedures or activities will be performed until each patient is fully informed about the study and the ICF is properly signed and dated. An ICF template will be provided by the Sponsor or designee to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF will be reviewed by the Sponsor and/or its designee before IRB submission. Once reviewed, the ICF will be submitted by the Investigator or Sponsor/designee (as applicable) to the IRB, and when applicable to regulatory authorities, for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients to whom the change is applicable must sign the revised form. Reconsent will be needed before rescreening a patient.

Before enrollment, each prospective patient and/or her parent(s)/legal guardian(s) will be given a full explanation of the study and be allowed to read the IRB-approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient, parent(s), and/or legal guardian(s) will be asked to give consent/assent to participate in the study by signing the ICF.

The Investigator will retain the signed original ICF and give a copy of the signed original ICF to the patient or legal guardian.

Patients aged 12 through 17 years old may participate where permitted by applicable local regulations and IRB approval. All applicable laws and regulations regarding the informed consent of minors are to be strictly observed.

12.1.4 Study Discontinuation and Closure

The Sponsor reserves the right to modify or terminate the study at any time. Possible reasons for termination are unsatisfactory enrollment of patients, new scientific knowledge becomes known that makes the objectives of the study no longer feasible, efficacy or safety reasons, e.g., if the incidence of AEs in this study or another study using the same investigational product indicates there is a potential health risk for patients.

The Sponsor or designee will provide a written statement to the IRB and the relevant regulatory authority with the reasons for modification or termination of the study. If the study is terminated, a closeout visit will be performed at each active site at which study investigational product was received and at least

1 patient was screened, and applicable procedures will be carried out to close the trial site(s). The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit or the last contact by which study-related data is conveyed.

12.1.5 Potential Impact of the COVID-19 Pandemic

The DARE-BV1-001 study is being conducted while the United States is contending with the COVID-19 pandemic. In March 2020, the FDA released a document entitled "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency;" this document was then further updated on April 16, 2020. This guidance acknowledges various ways in which the pandemic could impact clinical trials, as per the following excerpt:

"FDA recognizes that the COVID-19 public health emergency may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures."

In addition to the need for sites to implement procedures to ensure the safety of its patients and staff, the sponsor and CRO study teams have taken additional steps to contend with the potential consequences of the pandemic. For example, there will be increased reliance on remote monitoring, and additional documentation will be maintained to track operational disruptions or other study issues secondary to the consequences of the COVID-19 pandemic. Additional details are provided in the study Clinical Management Plan.

12.1.6 Confidentiality and Privacy

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records shall be kept in a secure storage area with limited access. Clinical information shall not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the IRB, or applicable regulatory authorities (e.g., the U.S. FDA), or unless otherwise required by law.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.1.7 Future Use of Stored Specimens and Data

No laboratory specimens will be retained after the end of the study.

12.1.8 Key Roles and Study Governance

The Medical Monitor, or a designated backup, will serve as the primary contact for site medical questions related to the study.

12.1.9 Safety Oversight

The Medical Monitor, or a designated backup, will conduct periodic reviews of study safety data to identify any potential safety concerns.

12.1.10 Clinical Monitoring

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor shall visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and other contacts. At sites where in-person monitor visits are not feasible due to the COVID-19 pandemic, virtual monitor visits will be permitted. The monitor shall maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel. Remote monitoring of the eCRF will also be employed for this trial. Additional details regarding clinical monitoring can be found in the trial Clinical Management Plan.

All aspects of the study shall be carefully monitored, by the Sponsor or its designee, for compliance with applicable regulations.

12.1.11 Quality Assurance and Quality Control

This study shall adhere to U.S. FDA standards as well as other applicable local standards of conduct regarding quality assurance. All parts of the U.S. CFR applicable to clinical studies, including 21 CFR Parts 50, 56, and 312, must be followed, along with ICH E6 (R2).

Suitably qualified and trained clinical research personnel of the Sponsor or designee shall visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. The eCRFs and source documentation shall be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol and study procedures, applicable regulatory and GCP obligations, proper maintenance of records including study drug accountability records, correct administration of study drug including storage conditions, and accurate reporting of AEs. After data from the patient's records have been entered onto the database, they shall be reviewed and the data verified against the patient's source data (details of data verification, including the percentage of data fields requiring source verification, shall be documented in a Monitoring Plan). Any discrepancies shall be tracked by paper or electronically with an electronic audit trail.

The Sponsor, an independent auditor, or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

12.1.12 Data Handling and Record Keeping

Investigators and institutions involved in the study shall permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency (i.e., U.S. FDA or other regulatory agency) access to all study records.

The Investigator shall promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or designee.

12.1.12.1 Data Collection and Management Responsibilities

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation as part of the case histories. These source documents may include, but are not limited to, laboratory reports, histology reports, and ultrasound findings.

Investigative site personnel shall enter patient data into the eCRF. Clinical data management shall be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events will be coded using MedDRA and concomitant medication terms will be coded using the World Health Organization Drug Dictionary (WHO-DD).

12.1.12.2 Study Records Retention

Following completion of the study, the Investigator shall retain copies of the approved study protocol, ICF, relevant source documents, and all other supporting documentation related to the study according to the ICH guidelines.

If the Investigator can no longer maintain the archive of study records (i.e., due to retirement or relocation), the Sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records may not be destroyed without prior written consent from the Sponsor.

12.1.13 Protocol Deviations

A protocol deviation occurs when the patient, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Enrolling a patient into the study without securing proper consent
- Deviating from the protocol-defined study procedures

Certain protocol deviations may require the patient to be discontinued early from the study. The Sponsor, in conjunction with the Investigator, will determine if a protocol deviation should result in withdrawal of a patient.

Failure to comply with GCP guidelines will also result in a protocol deviation. It is the responsibility of the research sites to report all protocol deviations to their IRB according to IRB policy.

12.1.14 Publication and Data Sharing Policy

All information concerning the study supplied by the Sponsor to the Principal Investigator and not previously published is considered confidential. No data collected in this study will be presented or published without prior approval from the Sponsor.

12.1.15 Conflict of Interest Policy

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under U.S. FDA 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

12.2 PROTOCOL SIGNATURE PAGE - SPONSOR

Protocol Number:	DARE-BV1-001
Study Title:	A Phase 3 Multi-center, Double-blind, Placebo-controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis
Sponsor:	Daré Bioscience, Inc. 3655 Nobel Drive, Suite 260 San Diego, CA 92122
Version Number:	4.0
Version Date:	14 Aug 2020

This study will be carried out in compliance with the International Council for Harmonisation (ICH) E6 (R2) guidance on Good Clinical Practice (GCP) and the United States (U.S.) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312).

Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol shall be conducted as described. All protocol deviations must be documented.

David R. Friend 08/20/2020

David Friend, PhD, Chief Scientific Officer, Daré Bioscience, Inc. *Date*

08/20/2020

Nadene Zack, MS, Vice President, Clinical Operations, Daré Bioscience, Inc. *Date*

12.3 PROTOCOL SIGNATURE PAGE – PRINCIPAL INVESTIGATOR

Protocol Number:	DARE-BV1-001
Study Title:	A Phase 3 Multi-center, Double-blind, Placebo-controlled, Randomized Study of DARE-BV1 in the Treatment of Bacterial Vaginosis
Sponsor:	Daré Bioscience, Inc. 3655 Nobel Drive, Suite 260 San Diego, CA 92122
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Except for a change that is intended to eliminate an immediate hazard to patients, the approved protocol shall be conducted as described. All protocol deviations must be documented. Any protocol-related issues that pose an immediate or significant hazard to patients must be reported to the Sponsor or designee.

_____

Principal Investigator Name (Print)

_____

Principal Investigator Signature *Date*

13 REFERENCES

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