Protocol DARE-BV1-001

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

Statistical Analysis Plan

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
BV	Bacterial Vaginosis
CC	Clinical Cure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel test
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ED	Early Discontinue
HEC	Hydroxyethylcellulose
HEENT	Head, Eyes, Ears, Nose and Throat
IRT	Interactive Response Technology
ITT	Intent-To-Treat
KOH	Potassium Hydroxide
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
Min	Minimum
MITT	Modified Intent-To-Treat
MNAR	Missing Not At Random
PK	Pharmacokinetics
PKS	Pharmacokinetics Subset (population)
PP	Per-Protocol
PT	Preferred Term
QD	One a day (from the Latin quaque die)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
STI	Sexual Transmitted Infection
TOC	Test Of Cure
TEAE	Treatment Emergent Adverse Event
WHO DDE	World Health Organization Drug Dictionary Enhanced

1.0 INTRODUCTION

The purpose of this document is to detail the planned statistical analysis and data presentations that will be performed to support the Clinical Study Report (CSR) for Daré Bioscience study protocol DARE-BV1-001. The analyses detailed herein are based on the study protocol (Version 4.0, dated 14AUG2020) and electronic case report forms (eCRFs, dated 24JUL2020). Any post-hoc or unplanned analyses not identified in this statistical analysis plan (SAP) will be clearly identified in the CSR.

2.0 PROTOCOL SUMMARY

2.1 Background

Bacterial vaginosis (BV) is a common bacterial infection in postmenarchal women. BV is typically diagnosed using Amsel's criteria (Amsel 1983). The four Amsel's criteria used to determine a clinical diagnosis of BV are as follows:

a) homogenous, non-viscous, off-white (milky or gray) thin discharge;
b) the presence of > 20% clue cells;
c) vaginal pH > 4.5;
d) positive "whiff" test ("fishy" odor of the vaginal discharge with the addition of a drop of 10% potassium hydroxide [KOH]).

Currently, oral and intravaginal metronidazole, intravaginal clindamycin, oral tinidazole, and oral secnidazole are used as the treatment of BV in the United States. 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, Alur, & Johnston, 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 pharmacokinetics (PK) data from a subset of participants. Research has shown that effective drug delivery is essential to optimize the therapy for BV.

2.2 Objectives

The primary objective of this 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 subjects with Clinical Cure at the test of cure (TOC) visit (Day 21-30). Clinical cure is defined as:

- Resolution of the 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.

The secondary efficacy objectives of the study include assessment of Bacteriological Cure and Therapeutic Cure of BV (defined in Section 2.4.2) and the safety and acceptability of DARE-BV1 (listed in Section 3.7.3) in postmenarchal females.

2.3 Trial Design

This is a multicenter (with approximately 36 study sites), randomized, double-blind (for both subjects and investigators), placebo-controlled study of DARE-BV1 clindamycin

phosphate vaginal gel, 2% (QD × 1 day) compared to placebo vaginal gel (hydroxyethylcellulose [HEC] Universal Placebo Gel) (QD × 1 day). Total 240 Subjects 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 TOC visit (or a Day 21-30 Safety Follow-up phone call for subjects who are prematurely discontinued). The total study duration will be up to approximately 30 days for a subject, with a minimum age of 12 years old. Females of 12 to 17 years old may participate where permitted by applicable local regulations and Institutional Review Board approval, also with consent from the parent(s)/guardian(s) and assent from themself.

Eligible subjects will be randomly assigned, stratified by study site and subject race (either African American or Not-African American), via Interactive Response Technology (IRT, by Suvoda LLC, Conshohocken, Pennsylvania) to one of the following treatment groups in the ratio of 2:1 of either:

A. clindamycin phosphate vaginal gel, 2% (DARE-BV1; 1 dose is 5 g gel = 100 mg clindamycin) QD × 1 day, or
B. placebo vaginal gel (Universal HEC Placebo Gel), 5 g, QD × 1 day.

Assigned product will be applied intravaginally within 1 day of randomization.

Approximately 20 subjects at selected study sites (1-3 sites are anticipated) will participate in a PK study. The subjects in this subset will apply the study drug at the study clinic during Visit 1 (randomization) 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 (±1 hour), 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.

All procedures and assessments associated with each study visit are shown in the Appendix 5.1 of this SAP.

2.4 Study Efficacy Endpoints

2.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with Clinical Cure at the TOC visit (Day 21-30). Here Clinical Cure is defined as all of the following 3 criteria being met:

- Resolution of abnormal vaginal discharge associated with BV,
- Negative 10% KOH whiff test,
- Clue cells < 20% of the total epithelial cells in the saline wet mount.

2.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

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

- Proportion of subjects 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).
- Proportion of subjects with Bacteriological Cure (Nugent score < 4) at the Interim Assessment visit (Day 7-14).
- Proportion of subjects with Therapeutic Cure at the Interim Assessment visit (Day 7-14).

2.5 Sample Size Consideration

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. Under the assumption that the Clinical Cure rates of 55% for DARE-BV1 and 30% for placebo, a sample size of 188 DARE-BV1 versus 94 placebo subjects will have 90% power to detect a statistically significant difference at a significance level of 0.05 (2-tailed). This sample size assumes 35% of randomized subjects will not be in the modified intent-to-treat (MITT) population (see Section 3.4 for analysis population definition) which is used for the primary efficacy analysis.

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Interim Safety Review

This is a short-duration study - a subject will be in the study for approximately 30 days. No formal interim analysis will be conducted for this short duration study.

3.1.2 Analysis Conventions

This section details general approaches to be used for the statistical analyses. Departures from these general approaches may be outlined in the specific detailed sections of this SAP, and will take precedence over the general approaches. The following approaches will be applied to all data presentations and analyses.

- Data listings will be provided for all CRF data with one listing for one CRF panel. All data listings will be sorted for presentation in the order of, treatment assignment, site identifier (ID), subject ID, and date of procedure or event.
- Statistical summary tables will be provided for most CRF data, and generated for each of the 2 treatment groups, and for all subjects (i.e., 2 groups combined, presented in a column labelled “Total”) when appropriate.
- Summary statistics will consist of the number and percentage of responses in each category for discrete (categorical) variables, and the number of non-missing observations (n), mean, median, standard deviation (SD), 25^{th}, 75^{th} percentiles, minimum, and maximum (abbreviated as “8-number statistics”) for continuous variables. Some parameters valued as integers (0, 1, 2, etc.) may be summarized as both categorical variable with counts and percentage of subjects and continuous variables with 8-number statistics.

- All mean values will be formatted to one more decimal place than the measured value, and standard deviation values will be formatted to two more decimal places than the measured value. For median values, the same decimal place as the measured values will be reported, if that is feasible without losing accuracy; otherwise, median values will be formatted to one more decimal place than the measured values.
- All percentages will be rounded to one decimal place. The number and percentage of categorical responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The denominator for percentage calculations will be the number of non-missing observations (n) when this number is shown, or will be the total sample size of the relevant treatment group for tables like adverse events, medical histories, or other tables where this number of non-missing observations (n) is not presented.
- All statistical tests will use a significance level of α = 0.05. Two-tailed tests will be performed for all analyses that use statistical testing.
- All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001', and p-values that round to 1.000 will be presented as '>0.999'. Any p-value $\leq$ 0.05 will be considered statistically significant and will be marked with one asterisk (e.g., 0.025*).
- All analysis and summary tables will have the population sample sizes in the column headings.
- Summary by visit tables will not include unscheduled visit(s); those unscheduled visit data will be included in relevant data listings.
- Baseline is defined as the last data point on or before the day of randomization.
- Calculating change from baseline to a visit will be performed as "Observed value at the visit – Baseline value". As a result of this approach, for those subjects who have only baseline, or conversely are missing a baseline value and only have a post-baseline value for a parameter, calculating Change from Baseline for that parameter at that visit will not be possible.
- Version 9.4 of SAS® or higher will be the statistical software package used to produce all statistical analysis tables and data listings.

3.2 Subject Disposition

Subject disposition will be summarized for ITT population as follows:

- Number of subjects who have signed informed consent in each of the following 3 groups for the All Screened population:
  - Screen failures
  - DARE-BV1
  - Placebo
- Summary of screen failures by the reason for ineligibility for screen failed subjects

- The number and percentage of randomized subjects who completed or discontinued prematurely from the study, the number and percentage of subjects who discontinued by each reason for all subjects.
- A listing of randomized subjects who discontinued prematurely from the study. The listing will include information about treatment assignment, study site ID number, subject ID number, age, number of days in the study (calculated as Date of Last Visit – Date of randomization + 1.), and reason for discontinuation.
- The number and percentage of randomized subjects at each study visit. This table will also be repeated for the MITT population.
- The number of randomized subjects who were enrolled, had completed, or discontinued prematurely at each study site.

The Disposition page of the CRF will be used to determine who discontinued prematurely from the study.

3.3 Protocol Deviations

Protocol deviations data, collected during the clinical monitoring process, will be classified into different types of deviations, such as informed consent process not conducted per ICH/GCP Guidelines, patient did not meet eligibility criteria, scheduled visit completed out of specified window, deviation from protocol-defined procedure, clinical assessment not done, lab processing error, lab assessment not completed, use of prohibited medication, study medication not returned/lost, etc. These data will be summarized categorically with number and percentage of distinct subjects for each type of deviations by treatment group and all subjects. All deviations will be reviewed prior to database lock, and each will be prospectively designated as either “minor” vs “major” to define whether the deviation warrants excluding the patient from the Per Protocol Population.

3.4 Analysis Populations

All Screened Population: all subjects who signed Consent Form and screened at the study sites.

Intent-to-Treat (ITT) Population: All randomized subjects.

Safety Population: All randomized subjects who applied assigned study drug. If the drug accountability is unknown (e.g., due to being lost to follow-up after being randomized) the subjects will be assumed to have taken study drug and included in the safety population. Subjects with confirmation of 0 doses taken will be excluded.

Pharmacokinetic Subset (PKS) Population: Safety population subjects who are enrolled into the PK sub-study and have at least one post-baseline PK measurement.

Modified Intent-to-Treat (MITT) Population: All Safety population subjects 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 (https://www.fda.gov/media/129530/download). If the Nugent score at baseline is missing, then the subject is excluded from the MITT population.

Per Protocol (PP) Population: subjects in MITT population who either receive other BV therapies during the study for any reason, or meet the following criteria:

1. Meet all 4 Amsel's criteria at screening
2. Apply assigned 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 subject receives other BV therapy for any reason, the subject will be included in the analysis as a treatment failure for all visits on or after receipt of the other BV therapy. Subjects 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 efficacy endpoints and cause a subject to be excluded from the PP population. Safety endpoints will not be impacted.

3.5 Demographics and Pre-Treatment Characteristics

Subject demographics and pre-treatment characteristics will be summarized for the ITT population, and some of these summaries may also be done for other populations, such as MITT and PP populations, when deemed important.

3.5.1 Demographics

A summary of demographics and subject characteristics will be created for the ITT, MITT, and PP populations, and include age, race, ethnicity, height, weight, and body mass index (BMI) at the screen visit with:

- 8-number statistics (number of non-missing observations, mean, median, SD, 25th percentile, 75th percentile, minimum, and maximum) for age, height, baseline weight, baseline BMI by treatment group and for all subjects.
- Age will also be categorized as ≤ 20, 21-30, 31-40, 41-50, ≥ 51, and then summarized categorically along with race, ethnicity.
- BMI at the study entry visit, which will also be categorized as: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥ 30.0). The number and percentage of subjects in each of these categories will be presented by treatment group and for all subjects.

3.5.2 Medical History

Medical history data will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. The codings will be reviewed by qualified medical personnel, and then summarized by system organ class (SOC) and preferred term (PT) and by the medical history status "Ongoing", or "Resolved" by treatment group and for all subjects in the ITT population. If a subject reports the same SOC/PT more than once in a status, that subject will be counted only once toward that status.

3.5.3 BV History

BV history data will be summarized categorically for the following parameters for ITT and MITT populations:

- Number of previously diagnosed BV episodes - lifetime (≤10, >10.),
- Number of previously diagnosed BV episodes in the past 12 months (≤3, >3),
- Treatment used in the last 12 months (Metronidazole vaginal, Metronidazole oral, Clindamycin vaginal, Clindamycin oral, Secnidazole, Tinidazole, Don't remember, or Other),

and also summarized with 8-number statistics, with n (number of non-missing), mean, SD, median, tertiles (33.3th and 66.7th percentiles), minimum, and maximum for:

- Number of previously diagnosed BV episodes - lifetime
- Number of previously diagnosed BV episodes in the past 12 months
- Approximate number of years since last diagnosed BV episode.

The last parameter "Approximate number of years past since last diagnosed BV episode" = 2020 – "Year of previous (last) BV episode" in BV CRF; but if the Year of previous (last) BV episode = 2020, this will be expressed as a fraction based on the number of months since last BV episode (e.g., 0.3 for 3.6 months), instead of as a whole number of 0.

3.5.4 Sexual, Contraceptive, and Pregnancy History

Gynecological history data will be summarized for key parameters collected in the CRFs, with categorical (qualitative) parameters as follows for ITT populations:

- What sanitary products does the subject currently use? (Tampons, Sanitary Pads, Menstrual cup, and Other, in Demographics CRF)
- Subject sexually active
- Previously diagnosed with other sexually transmitted infections
- Form of contraception to be used during the study (Oral contraceptive, Hormonal contraception (transdermal or implanted), Intrauterine device (IUD), Non-polyurethane condom, Vasectomy of partner, Abstinence, Surgically sterile, Postmenopausal, Other, or None)
- Had previous pregnancies
- Number of previous pregnancies (0, 1, 2, etc.)
- Number of C-sections and vaginal deliveries

and continuous (quantitative) parameters as:

- Approximate length of menstrual cycle (in days)
- Number of previous pregnancies
- Number of current sexual partners

The number and percentage of subjects will be provided by treatment group and for all subjects for each response to the question for categorical data, and 8-number statistics for continuous data.

3.5.5 Prior Medications

All medications taken by the subject during the 30 days prior to randomization (pre-study) and during the study will be recorded on the prior and concomitant medication CRF page. Prior medications are medications that were taken during the 30 days before randomization, and concomitant medications are medications taken after randomization.

Medications will be coded to the therapeutic drug classes and preferred names by using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE) B3 March 2020 version. The codings will be reviewed by qualified medical personnel, and then summarized by treatment group and for all subjects with the number and percentage of ITT subjects who had prior medications that were coded to each preferred name and therapeutic drug class (Level 2), as well as the number and percentage of subjects who had at least one prior medication. Subjects reporting more than one drug in each drug class/generic name are only counted once to that drug class/generic name.

Prior medications will be also be summarized by the descending order of frequencies (total number of ITT subjects) for drug class (i.e., no preferred names provided).

3.6 Concomitant Medications

As defined in the above Section 3.5.4, concomitant medications are medications taken on or after the subject applied study treatment. Similar to prior medications, concomitant medications will be summarized for Safety populations by the number and percentage of subjects in each coded drug name (preferred name) and drug class. They will also be summarized by the descending order of frequencies (total number of subjects with DARE-BV1 and placebo groups combined) for drug class (i.e., no preferred names provided).

A medication may be both “prior” and “concomitant” if a subject took it prior to the study product use (pre-study) and also used it again on/after study product use. Another summary table with unique number and percentage of subjects for each treatment group and all subjects will be presented for medications belonging to both “prior” and “concomitant” (i.e., a medication will not be included in the table unless a subject took it before randomization as well as on or after randomization).

3.7 Efficacy Analyses

The primary efficacy analyses will be conducted on the modified intent-to-treat (MITT) population. Additionally, efficacy analyses will be performed on the ITT and per-protocol (PP) population and will be considered supportive.

3.7.1 Primary Efficacy Analyses

The primary efficacy endpoint of this study is the proportion of Clinical Cure (CC) at the TOC visit (Day 21-30). CC is defined using the criteria of following 3 parameters from the Study Procedure CRF:

- *Abnormal Vaginal discharge consistent with BV, defined as presence of off-white (milky or gray) thin homogenous discharge, should have value of “No”,*
- *10% KOH whiff test, which is from the variable Whiff test, should have value of “Negative”,*

- *Clue cells < 20% of the total epithelial cells in the saline wet mount, which is from the variable Percentage of Clue Cells, and should have value below 20.*

The Clinical Cure will be "Yes" when all of the above 3 conditions are met; otherwise Clinical Cure will be "No" (this includes data missing in one or more of these 3 components). A Cochran-Mantel-Haenszel (CMH) test, stratified by study center and race (African-American/Black versus all others), will be performed to test the association between Clinical Cure and treatment assignment (either DARE-BV1, or placebo) for the subjects in MITT population. Subjects who received other BV therapy for any reason will be included in the analysis as a treatment failure (Clinical Cure will be "No") for all visits on or after receipt of the other BV therapy. Additionally, non-study treatments that might interfere with the assessment of the subject's BV will cause the subject to be analyzed as a treatment failure for all visits on or after receipt of the non-study treatment. The following non-study treatments will be considered to interfere with BV assessments and will cause a subject to be a failure on or after receipt of the non-study treatment:

- metronidazole
- tinidazole
- secnidazole
- clindamycin
- Intravaginal probiotics
- Intravaginal boric acid

If the p value from CMH (general association) chi-square test is ≤ to 0.05, then we will reject the null hypothesis that the 2 Clinical Cures rates in DARE-BV1 and placebo groups are equal.

A 95% confidence interval (CI), using Yates' correction, for the difference, $p_T - p_R$, in proportion of subjects achieving Clinical Cure will be calculated.

Furthermore, 2-sided 95% CI for the Clinical Cure rate of each individual treatment group, estimated as p_T and p_R for DARE-BV1 and placebo, respectively, will also be presented by using PROC FREQ in SAS®.

Sensitivity Analysis by Multiple Imputation for Missing Data

If some of the 3 components of Clinical Cure are missing, conventional analysis method only uses complete cases, which would reduce the sample size. Multiple Imputation (MI) is a way to make use of all records, including partially complete records. The imputed values are drawn from a distribution, so they inherently contain some variation. It replaces each missing variable with acceptable values, representing a distribution of possibilities. Here are the 3 parameters that will be missing for subject who prematurely discontinued study, and all are categorical variables.

- *Abnormal Vaginal Discharge consistent with BV (Yes, No)*
- *Whiff test (Negative, Positive)*
- *Less than 20% of clue cells (Yes, No, derived from the quantitative value)*

MI is a simulation-based procedure. Its purpose is to handle missing data to achieve valid statistical inference. First, the methodology is described, and then SAS code fragments will be provided. MI involves 3 steps:

a. Running an imputation model defined by the chosen variables to create imputed datasets. In other words, the missing values are filled in *m* times to generate *m* complete datasets.
b. The *m* complete datasets are analyzed by using standard procedures.
c. The parameter estimates from each imputed dataset are combined to get a final set of parameter estimates.

The aforementioned method for non-missing data will be repeated *m* times by using *m* imputed datasets for each of the 3 parameters that make up Clinical Cure. Then a final Clinical Cure will be determined for each imputation for each subject by combining the datasets for the 3 clinical cure parameters. The multiple imputation solves the limitations of single imputation by introducing an additional form of error based on variation in the parameter estimates across the imputation, which is called "between imputation error". The final results will be summarized by MIANALYZE Procedure in SAS®. The number of imputations will be determined once the number of subjects with missing Clinical Cure at Day 21-30 Visit is known. The decision on the number of imputations will be determined prior to database lock and unblinding. The number of imputations performed will be equal to the percentage of missing data to target a 99% imputation efficiency rate (e.g., if 10% of the subjects have missing data then 10 imputations will be performed: https://documentation.sas.com/?docsetId=statug&docsetTarget=statug_mi_details54.htm&docsetVersion=14.3&locale=en).

Imputation is only being done within each treatment group (since the treatment group variable is a factor in the modeling) because assigned drug dosing is complete for each subject once the subject takes 1 dose of study drug. Parameter Race is used as randomization strata, it will also be used in the MI process as a factor in the modeling.

Missing data in subjects who prematurely discontinue from the study will be designated as either missing at random (MAR) or missing not at random (MNAR), depending on the relationship between the subject's treatment with study drug (i.e., its effectiveness, safety and/or tolerability) and her reason for early discontinuation (ED). The sponsor and CRO will conduct a careful review of each discontinued subject's CRF data, in blinded way, i.e., before unblinding the randomization codes, to ensure that the ED reason is appropriately categorized; this review will include a review of AEs, efficacy data, medical history and medication usage in addition to the ED reason. However, for subjects discontinued study due to treatment failure, the analysis value for CC will be imputed as "No", and none of the 3 individual components will be separately imputed.

Any drop out reason can fall into either of the following two scenarios:

- Subjects prematurely discontinued due to reasons that are related or potentially related to their use of study drug will be assumed to be missing not at random (MNAR); these will include the CRF-defined ED reasons of "Occurrence of other vaginal infection requiring treatment" and "Other Adverse Event" if/when the causality designation is "Probably Related", "Possibly Related", or "Definitely Related" to study treatment.
- The remaining CRF-defined ED reasons will be assumed to be missing at random (MAR), including: "Retrospective discovery of an entry criterion violation;" "Pre-existing condition or abnormality, including abnormal laboratory or microbiological

result obtained at screening;" "Other adverse event" with causality = "Unrelated;" "Withdrawal of consent;" "Lack of compliance;" "Lost to follow-up;" and "Other."

The current COVID-19 pandemic may also impact subjects' ability to complete the study for reasons unrelated to the efficacy, safety, or tolerability of the study treatment. In the event that a subject must discontinue specifically due to a COVID-19-related illness, an ED reason of AE (causality = unrelated) will be recorded, and hence assumed to be MAR. In the event a subject must discontinue due to other consequences of the pandemic (e.g., illness in a close family member necessitating self-quarantine, or changes in the investigative site's ability to conduct business), then other MAR reasons will be utilized as appropriate (e.g., Other). In all such cases, reference to COVID-19 will be made in the CRF (or the study's deviation log, if appropriate) to ensure that the impact of the pandemic can be understood and characterized.

The complete data will be pooled from the 2 different missing pattern's imputation as the input data for efficacy analysis. First, we make the observed data into two subsets:

1) one subset with completers and early terminated subjects with termination reasons considered to be MAR,

2) the other with completers and early terminated subjects with termination reasons considered to be MNAR.

Note that we need to use completers, i.e., those not missing values for the clinical cure at Day 21-30, in both subsets to predict the missing values. Overlap data from completers (same data appear in both subsets) will be removed when pooling all together after separately running MI process for the above two subsets.

If there are subjects with a missing result at the Interim Assessment visit (Day 7-14) and a result at the TOC visit (Day 21-30), then the MCMC procedure within PROC MI will be used to turn the arbitrary missing patterns to monotone missing patterns under MAR assumption (https://www.pharmasug.org/proceedings/2019/ST/PharmaSUG-2019-ST-103.pdf).

Here are SAS® code fragments of the first subset data (with MAR) by PROC MI (https://documentation.sas.com/?docsetId=statug&docsetTarget=statug_mi_syntax09.htm&docsetVersion=14.3&locale=en) for Clinical Cure parameter "*Whiff Test*":

```
PROC MI data=Observed1 out=Imputed1 seed=s nimpute=m;
CLASS Trt01PN Race WHIFF_Day7_14 WHIFF_Day21_30;
MONOTONE logistic(WHIFF_7_14 = Trt01PN Race);
MONOTONE logistic(WHIFF_21_30 = WHIFF_7_14 Trt01PN Race);
VAR Trt01PN Race WHIFF_Day7_14 WHIFF_Day21_30;
RUN;
```

where *WHIFF_Day7_14* and *WHIFF_Day21_30* is the "*Whiff Test*" at Interim Assessment visit (Day 7-14) and TOC visit (Day 21-30), respectively; *s* is a randomization seed; *m* is the number of imputations (to be determined prior to database lock once the number of subjects without a clinical cure at day 21-30 is known); *Trt01PN* is the treatment group

indicator (1 for DARE-BV1, 2 for Placebo); *Race* is indicator (either “African-American”, or “Not- African-American”).

SAS codes for the second subset, missing not at random (MNAR):

PROC MI data=Observed2 out=Imputed2 seed=s nimpute=m;
CLASS Trt01PN Race WHIFF_Day7_14 WHIFF_Day21_30;
MNAR MODEL (WHIFF_Day7_14 WHIFF_Day21_30 / MODELOBS=CCMV);
MONOTONE logistic(WHIFF_Day7_14 = Trt01PN Race);
MONOTONE logistic(WHIFF_Day21_30 = WHIFF_Day7_14 Trt01PN Race);
VAR Trt01PN Race WHIFF_Day7_14 WHIFF_Day21_30;
RUN;

For the first subset, there is no need to use MNAR statement for this part of the data. This way we impute missing values using MAR assumption for each treatment group separately.

Similarly, the MI process will be done for the other 2 parameters - *Vaginal discharge, and Percentage of Clue Cells*. The primary endpoint Clinical Cure will be calculated from the 3 parameters, and the analysis for complete cases (no missing values) will be performed as aforementioned by using each of the *m* data sets. Final summary of the analysis result will utilize MIANALYZE Procedure in SAS®.

3.7.2 Secondary Efficacy Analyses

Regardless of the outcome and conclusion from the primary efficacy endpoint, the following secondary efficacy analysis tables will be presented. Statistical testing of the secondary efficacy endpoints will only be done if the p-value for the primary endpoint is ≤0.05. Hypothesis testing for the secondary efficacy endpoints will be conducted in a sequential manner to control the overall Type 1 error rate in the order presented below:

1. Proportion of MITT subjects with Clinical Cure at the Interim Assessment visit (Day 7-14).
2. Proportion of subjects in the MITT population with Bacteriological Cure at the TOC visit (Day 21-30). Bacteriological Cure is defined as a Nugent score < 4.
3. Proportion of MITT subjects 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).
4. Proportion of MITT subjects with Bacteriological Cure (Nugent score < 4) at the Interim Assessment visit (Day 7-14).
5. Proportion of MITT subjects 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 subjects 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 treatments) as well as non-study treatments that might interfere with the assessment of the subject’s BV (as outlined in Section 3.7.1

above) will cause the subject to be analyzed as a treatment failure for all visits on or after receipt of the non-study treatment.

The ITT and PP populations will be used to perform sensitivity analyses of the above primary and secondary efficacy analyses. Subjects in the PP population without a Clinical Cure result at Day 21-30 will be excluded from the PP analyses thus no imputation as a failure due to missing results (i.e., CC = "No") will be used for the PP analyses.

Nugent score will also be summarized categorically by its raw score (0, 1, 2, …,10). All results from the Amsel's 4 criteria will also be summarized categorically ("Yes"/ "No") by study visit and treatment group for both MITT and PP populations. Clue cell summary of "Yes"/"No" response will be derived using the percentage of clue cells and will be presented as <20 being the Yes response and ≥20 being the No response.

3.8 Safety Analyses

All safety analyses will be performed for the Safety population, and summaries will be presented by treatment group and all subjects, unless noted otherwise.

3.8.1 Treatment Exposure and Compliance

Each eligible subject should apply only one dose of the assigned drug, either (active) DARE-BV1, or placebo gel. Compliance with use of the study drug will be verified through collection and assessments of dispensed weight and returned weight of study product via Investigational Product (IP) CRF. The number and percentage of subjects that have a tube weight change (between dispense and return) of <4 grams or >6 grams will be summarized.

3.8.2 Adverse Events and Serious Adverse Events

A treatment-emergent adverse event (TEAE) is any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency after the study treatment started. A serious adverse event (SAE) is any adverse event that results in any of the following outcomes: Death; immediate threat to life; inpatient hospitalization or prolongation of an existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; other serious (medical important) AEs. All AEs will be coded with system organ class (SOC) and preferred term (PT) from the MedDRA Version 23.0. The codings will be reviewed by qualified medical personnel.

Incidence of AEs and SAEs will be summarized by SOC and PT with the number and percentage of subjects with each SOC and PT by treatment group. The following tables will be presented:

- Overall number and percent of subjects with AEs without presenting SOC or preferred term, which includes AE severity (Unknown, Mild, Moderate, Severe), AE relatedness (Unrelated, Possibly Related, Probably Related, Definitely Related); SAE; Death, or discontinued study due to any AE
- AEs by SOC and preferred term
- Study product-related AEs (including Possibly Related, Probably Related, and Definitely Related) by SOC and preferred term

- AEs presented in descending order of frequency by preferred term (without showing SOC), in which the most frequent one appears at first, and least frequent one will appear in the last
- AEs by SOC and preferred term and by severity
- AEs by SOC and preferred term and by relatedness to the study product

All the above tables (except for where specified) are counting number of distinct subjects in each SOC and PT. Subjects reporting more than one AE/SAE in each PT will be counted only once to that PT, using the most severe intensity, for unique number of subjects counting, while "Unknown" intensity will be an independently counted. The only exception to this will be for the summary by relatedness to the treatment, where subjects will be counted only once using the strongest relatedness to the treatment for the purpose of counting distinct number of subjects. The same principle also will be applied to the summary at the SOC level.

An overall AE high-level summary table will also be provided (without showing SOC and PT) for Safety population with total number and percentage of distinct subjects by treatment group.

Another high-level summary table will present the counts of events (i.e., not distinct subjects) similar to the following chart for each treatment group.

Relatedness (to the study treatment)	AE Severity				
	Unknown	Mild	Moderate	Severe	Total # (%) of Events
Unrelated	xx	xx	xx	xx	xx (x.x)
Possibly Related	xx	xx	xx	xx	xx (x.x)
Probably Related	xx	xx	xx	xx	xx (x.x)
Definitely Related	xx	xx	xx	xx	xx (x.x)
Total # of Events	xx	xx	xx	xx	xx (100.0)

Note that percentages at "Total # (%) of Events" column are based on the number on the one where "(100.0)" is displayed. This AE summary table, populated for each treatment group and all Safety population subjects, provides the cross reference between every level of relatedness and severity. If there are not any AEs of "Unknown" severity in the final analysis data, this "Unknown" column will not be presented in the final table.

Two listing-style tables, one for SAEs, and the other for AEs that led to premature study discontinuation, will also be presented, with the details about the event onset date, resolved date, study day of onset since the study treatment (calculated as Onset Date – Study Product Use Date +1), severity, outcome, medical intervention needed for the AE, and relatedness to the study treatment, as well as other supportive data such as the subject's age and number of days on the study.

3.8.3 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
- Edema
- Petechiae
- Erosion/ulceration

Subjects will also be queried by the Investigator or designee for presence of the following symptoms either at the visit (for Randomization visit) or since the last visit (for post-treatment visits), and to do the severity rating (on the scale of 0 to 3 as described above) for:

- Burning/stinging
- Vulvovaginal Pain
- Pruritus (itching)

Summary will be the number and percentage of subjects in each treatment group with the categorical results of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe, for each of the 7 symptoms at each visit.

3.8.4 Vital Signs and Weight

Vital signs measurements, including pulse rate (heart rate), oral temperature, systolic and diastolic blood pressures will be presented. Weight and BMI (unit: kg/m^2) = weight (kg) / [height (m)] ^{2}, obtained at the screening visit only, will be summarized. BMI will be categorized as: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥30.0). Both numerical and categorical summaries for BMI will be presented. The 8-number summary statistics for continuous variables and their changes from baseline will be presented by study visit.

3.8.5 Physical Examination

A complete physical examination in body areas such as dermatological, respiratory, etc., will be performed at Visit 1, and a directed physical exam will be performed at Visit 3 and at the Early Discontinuation visit (if applicable).

If any “Abnormality” is reported, the examination result is “Abnormal”; otherwise, it is “Normal”. Number and percentage of subjects in the categories of “Normal” and “Abnormal” will be presented by visit and examined body area.

For “Abnormal” findings, clinical significance (either Clinically Significant, or Not Clinically Significant) will also be summarized categorically.

3.8.6 Pelvic Examination

Pelvic examination will be done at each study visit, evaluating the vulva, vaginal wall, and cervix, etc. The examination results are “Normal”, or “Abnormal”. Number and percentage of subjects in these categories will be presented by visit for each examined pelvic area.

For “Abnormal” results, a further question “Was the result clinically significant?” will also be summarized categorically (“Yes”, “No”).

A summary of shifts from Baseline will also be presented.

3.8.7 Hematology, Chemistry, and Urinalysis

Hematology and chemistry observed values and changes from screening to TOC visit (or early discontinuation visit) visit will be summarized by 8-number statistics. A summary of shifts from Baseline will be presented for each lab test parameter. The normal range for each parameter will be used to create categories of Low, Normal, or High. Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as High (Low), and any result within the lower and upper limits of normal will be categorized as Normal. The number and percent of subjects in each category (Low, Normal, or High) from Baseline to TOC visit (or early discontinuation visit) will be presented for each lab test parameter.

Urinalysis data will be summarized categorically with counts and percentages of subjects for discrete data and 8-number statistics for continuous parameters.

3.8.8 Safety Phone Follow-Up

Safety phone follow-up data will be summarized categorically for

1. Did safety follow-up phone visit occur? (Yes, No)
2. Did subject experience any additional adverse events since last visit? (Yes, No)
3. Did subject take any additional concomitant medications/therapies/procedures since last visit? (Yes, No)
4. Does subject report they currently have abnormal vaginal discharge consistent with BV symptom (milky or gray, thin, homogeneous discharge)? (Yes, No)
5. Does patient report they currently have a “fishy” or unpleasant vaginal odor? (Yes, No)
6. Subject experienced burning/stinging since last visit? (Absent, Mild, Moderate, Severe)
7. Subject experienced vulvovaginal pain since last visit? (Absent, Mild, Moderate, Severe)
8. Subject Experienced pruritus (itching) since last visit? (Absent, Mild, Moderate, Severe)
9. Subject requires additional follow-up for signs/symptoms of BV? (Yes, No)

Data from the 4th question’s sub-question “Number of days symptom present” will be summarized as a continuous parameter with 8-number statistics.

3.8.9 Other Safety Assessments

On-Study Conduct CRF data will be summarized categorically for:

- Did patient abstain from vaginal sexual intercourse and/or sexual activity since the last study visit? (Yes, No)
- Did menstruation occur between the previous and the current study visit? (Yes, No)
- What sanitary product(s) did the subject use, or is using? (Tampons, Sanitary Pads, Menstrual cup, Other)
- Subject currently on menstrual cycle (Yes, No)

Other study assessments, such as pregnancy tests, will be provided in data listings.

3.9 User Acceptability Assessments

3.9.1 User Acceptability Questionnaire

All treated subjects will provide responses to questions related to their experience with the study drug (e.g., ease of application, messiness or lack thereof, etc.) and overall product acceptability at the Interim and TOC/End of Trial visits (a subset of the questions asked at the Interim Visit will be repeated at the TOC/ET visit). Responses will be summarized categorically for Safety population subjects at each visit.

1. How would you describe the process of filling the applicator with the study drug? (Very easy, Fairly easy, Neither easy nor difficult, Fairly difficult, Very difficult)
2. How would you describe the process of putting the study drug into your vagina? (Very easy, Fairly easy, Neither easy nor difficult, Fairly difficult, Very difficult)
3. How would you describe the process of removing the applicator from your vagina? (Very easy, Fairly easy, Neither easy nor difficult, Fairly difficult, Very difficult)
4. How would you describe your overall experience with the study drug in terms of neatness of applying it? (Clean, Fairly clean, Neither clean nor messy, Fairly messy, Messy)
5. Did you experience leakage in the days following using the study drug? (If yes, answer question 5a. If No, skip to question 6 (Yes, No)

5a. When you experienced leakage, was it Bothersome, or Not Bothersome?

6. Have you used other vaginally applied BV products in the past? (Yes - answer question 6a, 6b and 6c), No (skip to question 7)

6a. Compared to all other vaginally applied products you have used for BV, your overall experience with the study drug is (Much better, Better, Neither better nor worse, Worse, Much worse)

6b. Compared to all other vaginally applied products you have used for BV; the study treatment is: Much cleaner, Slightly cleaner, Neither cleaner nor messier, Slightly messier, or Much messier?

6c. Compared to other vaginally applied BV drugs, the leakage experienced was (Much less bothersome, Less bothersome, About the same, More bothersome, Much more bothersome)

7. Considering your overall experience with the study drug treatment, were you (Very satisfied, Somewhat satisfied, Neither satisfied nor dissatisfied, Somewhat dissatisfied, Very dissatisfied)
8. How likely is it that you would recommend this treatment to a friend who has BV? (Very likely, Likely, Neither likely nor unlikely, Unlikely, Very unlikely)
9. How likely would you be to use this treatment again if it were available after the study and you had BV again? (Very likely, Likely, Neither likely nor unlikely, Unlikely, Very unlikely).

A subset of the same questions, as follows, is asked at TOC Visit, which will be summarized categorically too:

1. Considering your overall experience with the study drug treatment, were you? (Very satisfied, Somewhat satisfied, Neither satisfied nor dissatisfied, Somewhat dissatisfied, Very dissatisfied)
2. How likely is it that you would recommend this treatment to a friend who has BV? (Very likely, Likely, Neither likely nor unlikely, Unlikely, Very unlikely)
3. How likely would you be to use this treatment again if it were available after the study and you had BV again? (Very likely, Likely, Neither likely nor unlikely, Unlikely, Very unlikely).

3.9.1.1 Product Attribute Ranking

As part of the Acceptability Questionnaire, all treated subjects will also be asked to rank the following five attributes of the study product in the order of their preference from 1 to 5, with 1 being the attribute they liked the most and 5 being the least, at both Interim Assessment and TOC visits for

- One-time dosing
- Vaginal drug delivery to the site of infection versus taking something orally
- Clear gel versus a colored or opaque cream
- Odorless
- Resolved bothersome symptoms quickly

These ranking data will be summarized by 8-number statistics at the 2 visits.

3.10 Pharmacokinetics Analyses

PK analysis will not be done in this study and a separate PK study protocol will perform the PK analysis. All collected plasma and vaginal clindamycin concentration data will be presented in data listings.

4.0 REFERENCES

1. Amsel R, Totten PA, Spiegel CA, et al. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74(1):14-22.
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4. https://www.fda.gov/media/129530/download
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5.0 APPENDICES

5.1 Study Schedule of Assessments

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**	
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
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	X	X	X	X	X
KOH wet mount for microscopic yeast assessment[8]	X	X	X		X
Vaginal culture for *Candida* species[9]	X				
Collect sample/prepare slides for Nugent score[9]	X	X	X		X
Perform OSOM® test for *Trichomonas vaginalis*[9]	X				
Collect samples for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* NAATs[9]	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[10]		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, regardless of childbearing potential, 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.
[8] 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.
[9] 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 will be provided in the study procedures manual.
[10] Perform compliance assessment by weighing the returned used tube and recording the weight in the eCRF.

Additional Sampling for PK Subset Subjects

Visit	Visit 1	Visits PK1-PK5	Visit 2	Visit 3	Safety Phone Follow-up	Early Discontinuation
Visit Name	**Screening/ Randomization**	**PK1-PK5**	**Interim Assessment**	**Test of Cure**	**FU after Early Discontinuation + 5 days**	
Study Day(s)	**1**	**2,3,4,5,6**	**7-14**	**21-30**	**21-30**	
Plasma samples for clindamycin level	X	X	X (only at Day 7)			X (if within the first 7 days)

Visit	Visit 1	Visits PK1-PK5	Visit 2	Visit 3	Safety Phone Follow-up	Early Discontinuation
Visit Name	Screening/ Randomization	PK1-PK5	Interim Assessment	Test of Cure	FU after Early Discontinuation + 5 days	
Study Day(s)	**1**	**2,3,4,5,6**	**7-14**	**21-30**	**21-30**	
Vaginal samples for clindamycin concentration	X	X	X (only at Day 7)			X (if applicable)

5.2 Table of Contents for Data Display

Tables and data listings will be numbered according to the nomenclature used to support the final CSR.

5.2.1 Planned Tables

The format of each unique table is provided in a separate document of "Table Shells", but no data listing shells are provided. Final outputs may be slightly different in layout from that of illustrated in "Table Shells". The table shells will not be amended to match the actual tables in such cases.

Table Number	Table Title	Analysis Population
14.1.1	Summary of Subject Disposition and Reasons for Discontinuation	All Screened
14.1.1.1	Screen Failure Reason Summary	All Screened
14.1.2	List of Subjects Who Prematurely Discontinued the Study	ITT
14.1.3	Summary of Subject Disposition by Study Site	ITT
14.1.4	Number and Percentage of Randomized Subjects at Each Visit	ITT
14.1.4M	Number and Percentage of Randomized Subjects at Each Visit	MITT
14.1.5	Summary of Protocol Deviations	ITT
14.1.6	Summary of Analysis Populations	ITT
14.1.7	Demographics	ITT
14.1.7M	Demographics	MITT
14.1.7P	Demographics	PP
14.1.8.1	Medical History	ITT
14.1.8.2	Sexual, Contraceptive and Pregnancy History	ITT
14.1.8.3	BV History	ITT

14.1.8.3M	BV History	MITT
14.1.9.1C	Number and Percentage of Subjects with Prior Medication Use by Drug Class in Descending Order of Frequencies	ITT
14.1.9.1N	Number and Percentage of Subjects with Prior Medication Use by Preferred Name in Descending Order of Frequencies	ITT
14.1.9.1	Number and Percentage of Subjects with Prior Medication Use by Drug Class and Preferred Name	ITT
14.1.9.2C	Number and Percentage of Subjects with Concomitant Medication Use by Drug Class in Descending Order of Frequencies	Safety
14.1.9.2N	Number and Percentage of Subjects with Concomitant Medication Use by Preferred Name in Descending Order of Frequencies	Safety
14.1.9.2	Number and Percentage of Subjects with Concomitant Medication Use by Drug Class and Preferred Name	Safety
14.1.9.3C	Number and Percentage of Subjects with Prior Medications Also Used After the Study Treatment Applied by Drug Class in Descending Order of Frequencies	Safety
14.1.9.3N	Number and Percentage of Subjects with Prior Medications Also Used After the Study Treatment Applied by Preferred Name in Descending Order of Frequencies	Safety
14.1.9.3	Number and Percentage of Subjects with Prior Medications Also Used After the Study Treatment Applied by Drug Class and Preferred Name	Safety
14.2.1	Primary Analysis of Clinical Cure	MITT
14.2.1Sen	Sensitivity Analysis of Clinical Cure through Multiple Imputation Method	MITT
14.2.1T	Analysis of Clinical Cure for Intent-to-Treat Population	ITT
14.2.1Sen-T	Sensitivity Analysis of Clinical Cure through Multiple Imputation Method for Intent-to-Treat Population	ITT
14.2.1P	Analysis of Clinical Cure for Per-Protocol Population	PP
14.2.2	Summary of Clinical Cure, Bacteriological Cure and Therapeutic Cure at the Interim Assessment Visit	MITT
14.2.2T	Summary of Clinical Cure, Bacteriological Cure and Therapeutic Cure at the Interim Assessment Visit for Intent-to-Treat Population	ITT
14.2.2P	Summary of Clinical Cure, Bacteriological Cure and Therapeutic Cure at the Interim Assessment Visit for Per-Protocol Population	PP

14.2.3	Summary of Bacteriological Cure and Therapeutic Cure at the Test of Cure Visit	MITT
14.2.3T	Summary of Bacteriological Cure and Therapeutic Cure at the Test of Cure Visit for Intent-to-Treat Population	ITT
14.2.3P	Summary of Bacteriological Cure and Therapeutic Cure at the Test of Cure Visit for Per-Protocol Population	PP
14.2.4	Nugent Score and Amsel's Criteria Summary by Visit	MITT
14.2.4T	Nugent Score and Amsel's Criteria Summary by Visit for Intent-to-Treat Population	ITT
14.2.4P	Nugent Score and Amsel's Criteria Summary by Visit for Per-Protocol Population	PP
14.2.5.1	Summary of User Acceptability at the Interim Assessment Visit	Safety
14.2.5.2	Summary of User Acceptability at the Test of Cure Visit	Safety
14.2.5.3	Summary of Product Attribute Rankings	Safety
14.3.0	Treatment Exposure and Compliance	Safety
14.3.1.1	Overall Number and Percentage of Subjects with Adverse Events	Safety
14.3.1.2	Overall Number of Adverse Events by Severity and Relatedness to the Study Treatment	Safety
14.3.1.3C	Summary of Adverse Events by System Organ Class in Descending Order of Frequencies	Safety
14.3.1.3P	Summary of Adverse Events by Preferred Term in Descending Order of Frequencies	Safety
14.3.1.4	Summary of Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.5C	Summary of Adverse Events by System Organ Class and by Severity	Safety
14.3.1.5	Summary of Adverse Events by System Organ Class and Preferred Term and by Severity	Safety
14.3.1.6C	Summary of Adverse Events by System Organ Class and by Relatedness to the Study Treatment	Safety
14.3.1.6	Summary of Adverse Events by System Organ Class and Preferred Term and by Relatedness to the Study Treatment	Safety
14.3.2.1	List of Serious Adverse Events	Safety
14.3.2.2	List of Adverse Events that Led to Premature Study Discontinuation	Safety
14.3.5	Local Site Reaction	Safety

14.3.6	Vital Signs and Weight	Safety
14.3.7	Physical Examination	Safety
14.3.8.1	Pelvic Examination	Safety
14.3.8.2	Shift of Pelvic Examination from Baseline	Safety
14.3.9.1	Hematology Test Results and Changes from Baseline	Safety
14.3.9.2	Hematology Test Results and Shifts from Baseline	Safety
14.3.9.3	Chemistry Test Results and Changes from Baseline	Safety
14.3.9.4	Chemistry Test Results and Shifts from Baseline	Safety
14.3.9.5	Summary of Urinalysis	Safety
14.3.10	Summary of Safety Phone Follow-Up	Safety
14.3.11	Summary of On-Study Conduct Questions	Safety

5.2.2 Planned Data Listings

No data listing shells are provided. A data listing may be split into 2 or more sub-listings (as Part A, Part B, etc.) when there are too many columns (variables) and the labels are lengthy, thus it is difficult to fit all headers in the same page. All data collected during the course of this study, including eDiary, will be presented in data listings.

Listing Number	Listing Title	Analysis Population
16.2.1.1	Subject Information	All Screened
16.2.1.2	Inclusion/Exclusion Criteria Not Met	All Screened
16.2.1.3	Subject Disposition	All Screened
16.2.1.4	Subject Study Visits	All Screened
16.2.1.5	Reconsent	All Screened
16.2.2	Protocol Deviations	All Screened
16.2.3	Safety Subjects Excluded from MITT or PP Populations	Safety
16.2.4.1	Demographics	All Screened
16.2.4.2	Medical History	All Screened
16.2.4.3	BV History	All Screened
16.2.4.4	Sexual, Contraceptive, and Pregnancy History	All Screened
16.2.4.4	Prior and Concomitant Medications	All Screened
16.2.5.1	Investigational Product	Safety
16.2.5.2	On-Study Conduct	All Screened
16.2.6.1	Study Procedures	All Screened
16.2.6.2.1	User Acceptability at Interim Assessment Visit	Safety
16.2.6.2.2	User Acceptability at Test of Cure Visit	Safety

16.2.6.3	Unscheduled Assessments	All Screened
16.2.6.4.0	PK Samples	PKS
16.2.6.4.1	Plasma Clindamycin Levels	PKS
16.2.6.4.2	Vaginal Clindamycin Concentration	PKS
16.2.7.1A	Adverse Events – Part A	Safety
16.2.7.1B	Adverse Events – Part B	Safety
16.2.7.2	Local Site Reaction	Safety
16.2.8.0	Lab Samples	All Screened
16.2.8.1	Hematology	All Screened
16.2.8.2	Chemistry	All Screened
16.2.8.3	Urinalysis	All Screened
16.2.8.4	Nugent Scores	All Screened
16.2.8.5	Chlamydia and Gonorrhea	All Screened
16.2.8.6	Trichomonas Vaginalis	All Screened
16.2.8.7	Candidiasis	All Screened
16.2.8.8	eDiary	All Screened
16.2.9.1	Vital Signs	All Screened
16.2.9.2	Physical Examination	All Screened
16.2.9.3	Pelvic Examination	All Screened
16.2.10	Pregnancy Test	All Screened
16.2.11	Safety Follow-Up Phone Contact	Safety