CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 18-0017

Study Title:

A Randomized, Double-Blind, Placebo-Controlled Trial of TOL-463 Insert for Suppression of Bacterial Vaginosis (BV) [SUBVert]

NCT03930745

Version 1.0

DATE: 07MAR2022

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 18-0017**
Development Phase:	Phase II
Products:	TOL-463 Insert or placebo
Form/Route:	Self-insert vaginally twice-weekly for 12 weeks
Indication Studied:	Bacterial vaginosis (BV)
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	19AUG2019
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	07MAR2022
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ASCUS	Atypical Squamous Cells of Undetermined Significance
BV	Bacterial Vaginosis
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CMS	Clinical Materials Services
CoC	Certificate of Confidentiality
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
CTM	Clinical Trial Material
C. trachomatis	*Chlamydia trachomatis*
DCF	Data Collection Form
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EIC	Enrollment Informed Consent
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HPF	High-power field
HPV	Human Papillomavirus
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intent-to-Treat
KOH	Potassium Hydroxide
LDPE	Low-Density Polyethylene

List of Abbreviations *(continued)*

MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MOP	Manual of Procedures
N	Number (typically refers to participants)
NAAT	Nucleic Acid Amplification Test
N. gonorrhoeae	*Neisseria gonorrhoeae*
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OER	Office of Extramural Research
OHRP	Office for Human Research Protections
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PI	Principal Investigator
PID	Pelvic Inflammatory Disease
PP	Per-Protocol
PPROM	Preterm Premature Rupture of Membranes
PVC	Polyvinyl Chloride
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SIC	Screening Informed Consent
SOP	Standard Operating Procedure
STI	Sexually Transmitted Infection
SubI	Sub Investigator
TEAE	Treatment-Emergent Adverse Event
TOC	Test of Cure
T. vaginalis	*Trichomonas vaginalis*
US	United States
USP-NF	United States Pharmacopeia and The National Formulary
WBC	White blood cell
VVC	Vulvovaginal Candidiasis
V0	Visit 0, Screening
V1	Visit 1, Enrollment
V2	Visit 2, First Follow-up, weeks 1-4
V3	Visit 3, Second Follow-up, weeks 5-8
V4	Visit 4, Third/Final Follow-up, weeks 9-12

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Randomized, Double-Blind, Placebo-Controlled Trial of TOL-463 Insert for Suppression of Bacterial Vaginosis (BV)" (DMID Protocol 18-0017) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample Tables, Figures and Listings (TFL) planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables and figures. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

2.1. Study Background

Bacterial vaginosis (BV) and vulvovaginal candidiasis (VVC), collectively referred to as vaginitis, are the two most prevalent lower reproductive tract infections, affecting tens of millions of women annually in the United States (US) and far more globally. BV is characterized by a general depletion of specific Lactobacillus species that are necessary for maintaining vaginal health and a dramatic increase in commensal organisms, notably Gardnerella vaginalis and other anaerobes; a local inflammatory response to Candida species (primarily C. albicans) characterizes VVC. Although currently recommended regimens afford reliable symptom relief, recurrence probability within 6 months for BV and VVC are as high as 83% and 60%, respectively, [1-3] and in which the survival of resistant biofilm communities have been increasingly implicated. These failure rates represent an important public health concern because these infections are associated with a host of serious complications including increased risk of acquiring and transmitting human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) and adverse pregnancy outcomes, including preterm premature rupture of membranes (PPROM), preterm birth and low birth weight infants. [4-6]

2.2. Purpose of the Analyses

These analyses will assess the efficacy and safety of TOL-463 Insert as compared to placebo insert self-administered vaginally twice-weekly for 12 weeks in suppressing BV following successful induction with oral metronidazole or another CDC-recommended BV treatment, and will be included in the clinical study report.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To evaluate the clinical efficacy of a twice-weekly application of TOL-463 vaginal insert in suppression of BV in women with a history of recurrent BV (RBV) following successful induction with oral metronidazole or another CDC-recommended BV treatment.

3.1.2. Secondary Objectives

1. To evaluate the time to BV recurrence as defined by clinical criteria.
2. To evaluate the incidence of vaginal symptoms over study participation.
3. To evaluate acceptability of a twice-weekly application of TOL-463 vaginal insert in suppression of BV.
4. To evaluate the safety of TOL-463 vaginal insert compared to placebo, including the incidence of secondary VVC.

3.1.3. Exploratory Objective

To evaluate the performance of the BD Max Vaginal Panel in characterizing clinical and microbiologic outcomes of the intervention.

3.2. Endpoints

3.2.1. Primary Endpoint

Among participants with a history of BV and negative (<=2 Amsel criteria and asymptomatic) at enrollment, the proportion of participants with recurrent BV by V4 as defined by clinical cure [Study day 85-91].

Recurrence of BV at each follow-up visit is defined as > 2 of the following Amsel criteria:

a. Positive KOH whiff test
b. Homogeneous discharge characteristic of BV
c. Clue cells ≥ 20% of vaginal squamous epithelial cells
d. Vaginal pH > 4.5

3.2.2. Secondary Endpoints

1. Time to BV recurrence.
2. Proportion of participants reporting BV symptoms through the follow-up period.
3. Number of participants satisfied with the study treatment through the follow-up period.
4. The occurrence of AEs considered product-related following initiation of study treatment and through the final study visit.

5. The occurrence of culture confirmed secondary VVC following initiation of study treatment and through the final study visit.

3.2.3. Exploratory Endpoint

To evaluate the performance of the BD Max Vaginal Panel in characterizing clinical and microbiologic outcomes of the intervention.

3.3. Study Definitions and Derived Variables

Clinical Diagnosis of BV:

The clinical diagnosis of BV will be based on the presence of following 4 Amsel criteria by pelvic examination, where >2 is BV recurrence; and <= 2 is BV suppression:

1. Homogenous vaginal discharge characteristic of BV;
2. A fishy odor of the vaginal discharge with the addition of a drop of 10% KOH (positive whiff test);
3. Clue cells ≥ 20% of the total vaginal squamous epithelial cells on saline microscopy;
4. Vaginal fluid pH >4.5.

Nugent Criteria for Determination of BV:

A vaginal swab for microbiologic assessment of BV by Nugent criteria should be performed. The Nugent score utilizes a 0-10 point scale for evaluation of vaginal flora and is based on the weighted sum score of the following three bacterial morphotypes calculated from the slide exam under oil immersion (1000x):

1. *Lactobacillus*: Large Gram-negative rods
2. *Gardnerella*/*Bacteroides* spp: thin, curved, Gram-variable rods
3. *Mobiluncus* spp: thin, curved, Gram-variable rods

The Nugent score is interpreted as follows: 0-3 normal; 4-6 intermediate; and 7-10 BV. For the purposes of this study, a Nugent score of ≥7 will be used to define a microbiologic recurrence of BV for ancillary analysis.

Clinical Diagnosis of VVC:

A clinical diagnosis of VVC at V1-V4 will be based on a clinician's review of vulvovaginal signs (edema, erythema, and excoriation) and symptoms (itching, burning, and irritation) and a positive KOH microscopy with identification of yeast forms (hyphae/pseudohyphae) or budding yeasts.

***Candida* Culture for Determination of VVC:**

For participants with a clinical diagnosis of VVC at V1-V4, a vaginal swab should also be taken for confirmation of *Candida* by culture with speciation. Candida culture in the setting of incomplete criteria for the clinical diagnosis may be obtained at the discretion of the study clinician.

Study Completion and Early Termination

Completion, i.e., completed follow-up includes participants who remained BV suppressed and were followed-up through Visit 4 as well as participant whose participation ended prior to Visit 4 due to a clinical BV

diagnosis. Terminated Early includes participants who terminated from the study prior to Visit 4 for reasons other than a clinical BV diagnosis or for diagnosis with recurrent BV off study.

BD Max Vaginal Panel Performance Evaluation

Sensitivity = TP/(TP + FN) = (Number of true positives)/(Number of sick individuals in the population)

Specificity = TN/(TN + FP) = (Number of true negatives)/(Number of all well individuals in the population)

PPV=TP/(TP+FP) = (Number of true positives)/(Number of positive calls)

NPV=TN/(TN+FN) = (Number of true negatives)/(Number of negative calls)

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase II randomized, double-blind, placebo-controlled study screening approximately 600 adult females 18-55 years of age to enroll approximately 250 participants in total (125 per arm) to achieve 200 evaluable participants at the test of cure (TOC) visit. The study is designed to determine the clinical efficacy of an investigational product (IP), TOL-463 Insert, manufactured by Toltec Pharmaceuticals, in suppressing RBV when administered to women who have a history of RBV and have been successfully cleared of their current BV infection using oral metronidazole, 500 mg twice a day for 7 days or another CDC-recommended BV treatment.

Participants who consent to screening will have baseline clinical information collected at Visit 0, screening (Day -15 to -8), (V0). This information will consist of demographics, current vaginal symptoms, medical and sexual history, concomitant medications, and clinical and laboratory findings. Participants will undergo a pelvic examination and have vaginal specimens collected for confirmation of BV and for diagnostic testing for common STIs (*C. trachomatis, N. gonorrhoeae,* and *T. vaginalis*). Women with a clinical diagnosis of BV who meet all other screening Inclusion/Exclusion criteria will be treated with oral metronidazole, 500 mg twice a day for 7 days, or another CDC-recommended BV treatment, and scheduled for a Visit 1, enrollment, (V1) in 8 to 15 days. At the enrollment visit, women who test negative for BV, defined as ≤ 2 of 4 Amsel criteria and absence of symptoms of BV (absence of homogenous discharge and odor), will be offered to review and sign the Enrollment consent. Women who consent and qualify will be enrolled and randomized (1:1) to one of two groups (TOL-463 Insert or placebo). IP will be self-administered vaginally, twice-weekly for 12 weeks. Follow-up clinic visits will occur at Visit 2 (V2), Visit 3 (V3), and Visit 4 (V4). For women with cleared BV at enrollment, the primary endpoint will be clinical failure, recurrence of BV by V4.

Safety will be measured by participant report, targeted physical examination, and pelvic examination. All AEs will be collected through V4. Safety oversight will be provided by a Data and Safety Monitoring Board (DSMB).

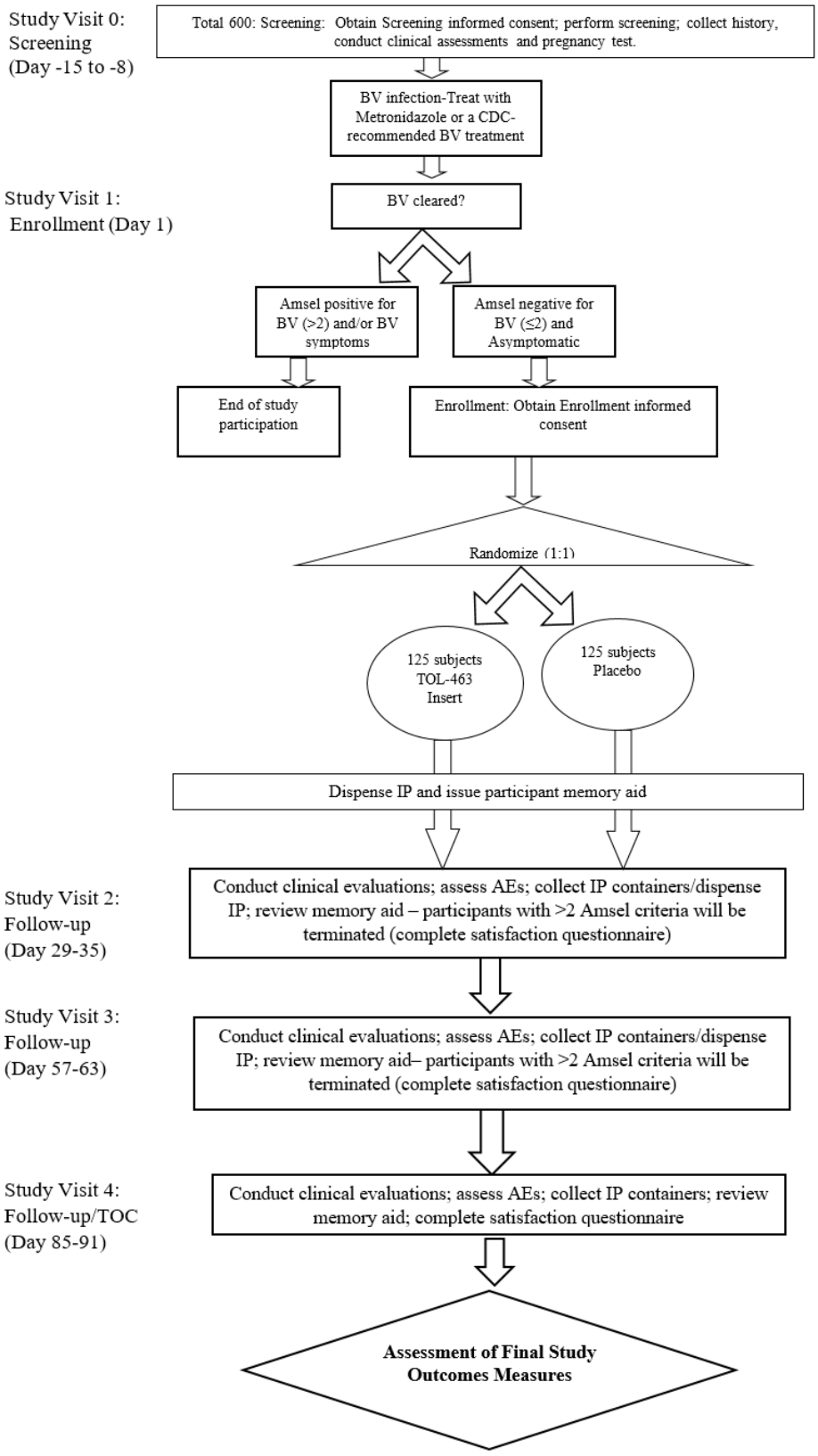
Laboratory testing will include urine pregnancy, nucleic acid amplification tests (NAATs) for chlamydia, gonorrhea, and trichomoniasis, and Gram stain for Nugent scoring, as well as assessment of vaginal pH, saline microscopy (clue cells, motile trichomonads, yeast forms), and KOH preparation at each site's local lab. *Candida* culture will be performed as clinically indicated. Polymerase Chain Reaction, PCR-based molecular diagnosis of BV through a multi-organism PCR algorithm on the BD Max Vaginal Panel will be performed at a certified laboratory for all scheduled study visits.

The duration of the study for participants who are enrolled and randomized will be approximately 100 days. For those not enrolled, participation will end at their V1, Day 1. Enrollment is expected to be completed in approximately eighteen months.

All participants will be asked to abstain from anal, receptive oral, and vaginal sexual intercourse within one hour of IP administration and for 24 hours after. Participants who are sexually active will be required to use an effective form of birth control during study participation through the final visit/V4. A simplified participant memory aid will be provided to study participants to document symptoms, AEs, and protocol compliance.

Figure 1 below presents the schematic of the study design and Table 1 presents the schedule of events.

Figure 1: Schematic of Study Design



4.2. Discussion of Study Design, Including the Choice of Control Groups

It is hypothesized that a twice-weekly application of TOL-463 vaginal insert will be clinically effective in suppressing BV in women with a history of RBV following successful induction with oral metronidazole or other CDC-recommended BV treatment. A placebo-blinded, randomized controlled trial is necessary to definitively evaluate the clinical efficacy of TOL-463 Insert. This trial aims to meet this need.

4.3. Selection of Study Population

This study will screen approximately 600 women 18-55 years of age who have recurrent RBV, defined as a current BV infection and at least two previous episodes of BV by documentation or self-report in the past year. Women who meet Screening eligibility will be treated with a standard course of oral metronidazole or another CDC-recommended BV treatment. Participants will return within approximately one week of completing the metronidazole treatment or other CDC-recommended BV treatment, for assessment of clinical cure. Clinical cure of BV is defined as ≤ 2 of 4 Amsel criteria and absence of reported symptoms of BV (i.e. no malodorous discharge consistent with BV).

Participants who return for the Enrollment Visit, V1 and are determined to be clinically cured will be offered to review and sign the Enrollment consent. Participants who consent and meet Enrollment eligibility will be randomized in a 1:1 ratio to twice weekly blinded suppressive therapy with TOL-463 or placebo. It is estimated that approximately 250 participants will be eligible for Enrollment with approximately 125 participants in each suppressive therapy group.

No exemptions will be granted on Screening or Enrollment eligibility criteria for this DMID- sponsored trial.

Participants will be recruited from health clinics in the U.S.

Those participants who enroll in the study will undergo up to 3 scheduled Follow-up visits to evaluate clinical diagnosis of BV at each visit. Participants who develop vaginal symptoms between scheduled visits will be asked to return for an unscheduled visit. If at any time during a follow-up visit a participant is diagnosed with clinical BV (> 2 Amsel criteria), the study endpoint of BV reoccurrence is met, and participation in the study will end.

The study will target a total of 200 evaluable participants.

4.3.1. Participant Inclusion Criteria

Women must meet all of the following inclusion criteria to be eligible for inclusion in the study.

4.3.1.1. Screening Visit(s) Inclusion Criteria

1. Women with a current BV infection and a history of at least two previous episodes of BV by documentation or self-report in the past year. V0 diagnosis is based on the presence of ≥ 3Amsel criteria*;

   *Homogeneous vaginal discharge; positive KOH whiff test; vaginal pH of > 4.5; and ≥ 20% clue cells.

2. Willing and able to provide written informed consent;
3. Age 18-55 years of age at the time of V0;
4. General good health based on medical history, targeted physical examination, and pelvic examination;

5. For participants 21 years of age or older, Pap test performed within the past 3 years, with the most recent result being normal or ASCUS HPV negative OR Pap smear collected at V0*;

   *Consistent with current Pap screening guidelines, a Pap smear must be performed at V0, for women who meet the following criteria and cannot provide documentation or self-report of a normal or ASCUS HPV negative Pap smear, conducted within the prior 3 years: (a) has not had a hysterectomy or (b) has had a hysterectomy and has a history of cervical intraepithelial neoplasia grade 2+ (CIN2+) in the past 20 years.
   Note: If a Pap smear is conducted at V0, the results are not required prior to enrollment.

6. Have a negative urine pregnancy test at V0, if of childbearing potential;
7. Must be of non-childbearing potential* OR must be using an effective method of birth control** and must be willing to continue the method through the end of IP administration.

   *Defined as post-menopausal, or status post bilateral tubal ligation, or status post bilateral oophorectomy or status post hysterectomy.
   **Acceptable methods are defined as:
   a. IUDs or hormonal contraceptives for at least 22 days prior to screening. Note: Intravaginal contraceptive rings (e.g., NuvaRing) are not acceptable forms of birth control for this study.
   b. Consistent use of a barrier method, including diaphragms or condoms, for at least 13 days prior to screening.
   c. Abstinence from vaginal sexual intercourse for at least 13 days prior to screening.
   d. Exclusively same-sex relationship.
   e. Monogamous relationship with vasectomized partner.

8. Willing and able to cooperate to the extent and degree required by this protocol at the discretion of the investigator.

4.3.1.2. Enrollment Visit Inclusion Criteria

In addition to confirming all relevant Screening Visit Inclusion Criteria, women must meet all of the following criteria to be eligible for enrollment in the study.

1. Willing and able to provide Enrollment written informed consent;
2. After completion of metronidazole induction therapy or another CDC-recommended BV treatment, no clinical evidence of BV* and absence of symptoms of BV** at V1;

   *As defined by ≤ 2 of 4 Amsel criteria.
   **Defined as absence of vaginal discharge and odor consistent with BV.

3. Must have a negative urine pregnancy test at V1, if of childbearing potential;
4. Willing to refrain from any intravaginal products/medications* other than the IP throughout the course of the trial;

   * For example: douches, antifungal or antibacterial preparations, lubricants, contraceptive creams, gels, foams, sponges, spermicides.

5. Must agree to abstain from receptive oral, anal, and vaginal sexual intercourse one hour prior to IP administration and for 24 hours after;
6. Willing to refrain from using tampons or menstrual cups for 24 hours after IP administration.

7. Must be of non-childbearing potential* OR must be using an effective method of birth control** and must be willing to continue the method through the end of IP administration.

   *Defined as post-menopausal, or status post bilateral tubal ligation, or status post bilateral oophorectomy or status post hysterectomy.
   **Acceptable methods are defined as:
   a. IUDs or hormonal contraceptives for at least 30 days prior to using IP. Note: Intravaginal contraceptive rings (e.g., NuvaRing) are not acceptable forms of birth control for this study.
   b. Consistent use of a barrier method, including diaphragms or condoms, for at least 21 days prior to using IP.
   c. Abstinence from vaginal sexual intercourse for at least 21 days prior to using IP.
   d. Exclusively same-sex relationship.
   e. Monogamous relationship with vasectomized partner.

4.3.2. Participant Exclusion Criteria

Women who meet any of the following exclusion criteria will be excluded from the study.

4.3.2.1. Screening Visit(s) Exclusion Criteria

1. Diagnosis of another vaginal or vulvar condition that may confuse interpretation of response to IP*;

   *For example: erosive lichen planus, desquamative inflammatory vaginitis, or contact dermatitis involving the vulvar epithelium.

2. Concurrent VVC infection with inability to be treated with oral fluconazole;
3. Infectious cause of cervicitis (e.g., *N. gonorrhoeae*, *C. trachomatis*, or *T. vaginalis*) confirmed on physical examination and/or with laboratory testing**[+];

   ** Women may be rescreened for eligibility following successful treatment of confounding STI.
   [+]Results of NAAT testing will be reviewed prior to enrollment.

4. Active genital lesions, including ulcers or vesicles consistent with herpes or warts;
5. Planned ongoing immunosuppressive therapy or systemic antibiotic treatment during the course of the study;
6. History of hypersensitivity, allergy or other contraindication(s) to metronidazole or other CDC-recommended BV treatment used to treat subject;
7. History of hypersensitivity to any TOL-463 formulation components (see IB for product information);
8. Current or untreated cervical intraepithelial neoplasia (CIN) or cervical carcinoma;
9. Currently pregnant or nursing;
10. Any other condition that, in the opinion of the investigator, would interfere with participation in the study;
11. Previous enrollment in the study or at the investigator's discretion.

4.3.2.2. Enrollment Visit Exclusion Criteria

In addition to confirming all Screening Visit Exclusion Criteria, women who meet any of the following criteria will not be eligible for enrollment in the study.

1. Active menses or significant vaginal bleeding as determined by the study clinician at V1*;

   * Note: women who are menstruating may be reevaluated for study enrollment within the enrollment window.
2. Use of vaginal or systemic antibiotic or antifungal since V0, other than oral metronidazole, CDC-recommended BV treatment, or oral fluconazole, as per protocol;
3. Evidence or suspicion of infectious cause of cervicitis or active genital lesion on pelvic examination at V1;
4. Concurrent VVC infection at V1 with inability to treat with oral fluconazole;
5. Use of any investigational drug within 30 days prior to V1 or planned/anticipated use during study participation.

4.4. Treatments

4.4.1. Treatments Administered

Participants will be randomized to one of two arms, as follows:

- TOL-463 Vaginal Insert: Self-administered vaginally as a single 2 g unit dose twice a week with a minimum of a two-day duration in between doses for twelve weeks with the aid of a disposable applicator.
- Placebo: Self-administered vaginally as a single 2 g unit dose twice a week with a minimum of a two-day duration in between doses for twelve weeks with the aid of a disposable applicator.

4.4.2. Identity of Investigational Product(s)

TOL-463 is a non-azole vaginal anti-infective drug candidate designed as a dual-indication therapy for BV and VVC. The product is formulated as a hydrophilic melt insert. All excipients are United States Pharmacopeia and The National Formulary (USP-NF) materials and are formulated at levels consistent with the acceptable use ranges specified within the FDA Inactive Ingredient Guide.

TOL-463 vaginal inserts and matching Placebo vaginal inserts will be supplied in 2.0 cc/g low-density polyethylene (LDPE) + polyvinyl chloride (PVC) plastic unit-dose insert molds with ten vaginal applicators.

Placebo Vaginal Inserts are manufactured and provided by Toltec Pharmaceuticals.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Participants will be randomized 1:1 to receive one of two treatments: TOL-463 vaginal inserts or Placebo vaginal inserts.

The list of randomized treatment assignments will be prepared by statisticians at the SDCC and included in the enrollment module of the Emmes' Internet Data Entry System (IDES). Advantage eClinical® will assign each participant to a blinded treatment number from the list after demographic and eligibility data have been entered. Each site will have a supply of blinded study drug kits pre-labeled with treatment numbers, each

containing sufficient doses to treat a participant for twelve weeks. The packaged study drug kits contain three, separate four-week kits to be dispensed to the participant at Enrollment V1 and Follow-ups V2 and V3 as applicable. Once a participant is assigned a treatment number, the corresponding kit will be distributed to the participant.

Instructions for using the enrollment module are included in the IDES User's Guide. Manual back-up randomization procedures are provided in the MOP for use in case the site temporarily loses Internet access, or the online enrollment system is unavailable.

The trial will use a site-stratified, permuted block randomization scheme. Permuted blocked randomization is used to avoid the potential for serious imbalance in the number of participants assigned to each group, which can occur in simple randomization procedures.

4.4.4. Selection of Doses in the Study

Participants will be randomized to one of two arms, as follows:

TOL-463 Vaginal Insert: Administered vaginally as a single 2 g unit dose twice a week with a minimum of a two-day duration in between doses for twelve weeks with the aid of a disposable applicator.

Placebo: Administered vaginally as a single 2 g unit dose twice a week with a minimum of a two-day duration in between doses for twelve weeks with the aid of a disposable applicator.

4.4.5. Selection and Timing of Dose for Each Subject

All subjects will receive TOL-463 Vaginal Insert or placebo administered vaginally as a single 2 g unit dose twice a week with a minimum of a two-day duration in between doses for twelve weeks with the aid of a disposable applicator.

4.4.6. Blinding

Participants, the study staff who dispense study drug and perform study assessments after study drug administration, data entry personnel at the sites, and laboratory personnel will be blinded to treatment assignment. The DSMB may receive efficacy data in aggregate and presented by treatment group, as specified in the DSMB charter. The DSMB may request to be completely unblinded to individual study drug assignments, as needed, to adequately assess SAEs.

Study drug will be prepared at Fisher BioServices in blinded numbered kits. All kits will look identical and contain an identical number of inserts. Emmes will provide an unblinded list identifying the treatment identity (TOL-463 or placebo) in each kit to the Fisher staff responsible for preparing study drug kits. Clinicians, investigators, and all blinded staff will not have access to this list until after the trial has ended.

4.4.7. Prior and Concomitant Therapy

Administration of any medications, therapies, or vaccines will be recorded on the appropriate DCF. Concomitant medications will include all medications taken 30 days prior to the initial screening visit V0, through V4 or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included, as well as herbs, vitamins, and supplements.

Participants who have received study IP and are subsequently diagnosed with a concomitant infection that requires systemic antibiotics will receive treatment according to the local clinic's standard protocols but will

be excluded from per-protocol analyses and terminated from the study. However, participants who have received study IP and are subsequently diagnosed with VVC can remain in the study and be considered evaluable for efficacy if they are appropriate candidates for oral fluconazole therapy.

At the discretion of the site PI, use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the IP should not be used unless absolutely necessary.

4.4.8. Treatment Compliance

The TOL-463 Insert and placebo are inserted by the study participant.

At each follow up visit, V2 through V4, participants will be asked to bring the study IP packaging, unused inserts (if any) and memory aid corresponding to the return visit (V2, V3 or V4) to the study personnel. Study personnel will review adherence to the study IP schedule with the participants, including the participant memory aid, and record this on the appropriate DCF at each follow-up visit and any unscheduled visits. Study personnel will record the number of unused inserts and empty packaging returned at each of the follow-up visits, V2 thru V4. Compliance with the study protocol will be assessed and documented by study personnel at each of the follow-up visits, V2 thru V4, and at any unscheduled visits. Study personnel may discard the participant's memory aid after documenting compliance.

The protocol defines that a participant is compliant with the study treatment if she misses ≤ 2 non-consecutive doses of IP per month, as assessed by participant memory aid and returned IP and packaging at each follow up visit (V2, V3, V4).

A blinded case review committee will review subjects' data to determine if they were compliant with the study treatment throughout the study, for cases that could not be determined programmatically. Subjects will be further excluded from per-protocol population analyses if they were not compliant with the study treatment throughout the study, see section 6.3 .

4.5. Efficacy (Immunogenicity) and Safety Variables

Multiple observations within specific visit period are acceptable. In the case of multiple observations within a specific window, the assessment value that is closest to the scheduled visit window will be used in the analyses for the post-baseline records. Whether to use and how to use the observations from early termination at an unscheduled visit along with the observations obtained at the corresponding scheduled visit will be specified in the applicable tables. For screening and baseline visits, the last assessment value will be used. All the recorded data will be listed. If observations have the same distance to the scheduled assessment, the latest one will be used.

4.5.1. Efficacy variables

The primary efficacy analysis estimates the clinical efficacy rate of TOL-463. At each follow-up visit, the Amsel criteria will be assessed, see definition in section 3.3 .

For the primary analysis, a participant is deemed to experience a recurrence of BV at a follow-up visit if >2 of the Amsel criteria are met or diagnosed of BV recurrence off site. A participant has clinical suppression of BV if she meets ≤ 2 of the criteria at each observed follow-up visit through V4. See below and section 6.5 for handling missing BV status by TOC (visit 4).

The proportion of participants with recurrence of BV (treatment failure) up to and including V4 will be summarized overall and by treatment group along with two-sided 95% Wilson CIs. The primary analysis will be performed in the mITT analysis population. Secondary analyses of the primary outcome measure will be performed in the PP analysis population.

For the mITT analysis population, the BV status of subjects whose status cannot be determined by the TOC visit for any reason or those who withdrew or those who dropped out early will be considered 'treatment failure' for primary recurrence endpoint. For the PP analysis population, subjects whose BV status cannot be determined by the TOC visit for any reason will be excluded from the analysis. For secondary endpoints, missing values will be further excluded from the mITT and PP populations.

In addition, the rate of recurrence, which considers the amount of observed follow-up time for each participant, will be estimated within each treatment group along with corresponding 95% CIs. We will use a person-time approach as discussed in section 8.1.

Secondary efficacy analyses will be performed in the mITT and PP analysis populations.

For the analysis of Secondary Objective 1, the time to BV recurrence will be estimated by treatment group using Kaplan-Meier estimates. For participants who experience clinically diagnosed BV recurrence in study by V4, the time of BV recurrence will be defined as the midpoint between the earliest time point of a positive BV diagnosis (post-baseline) and the previous observed time-point. Subjects with BV recurrence diagnosed off study will be treated as missing time to BV recurrence and excluded from the analyses for secondary endpoints, as defined above and in Section 6.5. For participants without BV recurrence at or before V4, the BV recurrence endpoint will be coded as censored, with time to recurrence defined as the elapsed time from the first dose of IP, to the earliest of: V4 time-point, the last observed time-point prior to loss to follow-up, or the time-point at which the participant became ineligible for the particular analysis population.

For the analysis of Secondary Objective 2, the proportion of participants experiencing BV symptoms will be estimated overall, by symptom category, and by treatment group.

For the analysis of Secondary Objective 3, responses to the satisfaction questionnaire will be summarized overall and by treatment group. Categorical responses will be summarized using contingency tables.

Descriptions of the analyses to assess the exploratory objective as well as other analyses that will support the primary and secondary efficacy analyses will be provided in Section 8.4.

4.5.2. Safety variables

Safety will be monitored throughout the study by targeted physical and pelvic examination and participant reporting. Safety will be assessed by the frequency and severity of:

1. Serious AEs occurring after randomization and from the time of the IP dose through V4.
2. Non-serious AEs occurring after randomization and from the time of the IP dose through V4.

4.5.2.1. Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The

occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs not meeting the criteria for "serious adverse events" should be captured on the appropriated CRF. Information to be collected for AEs includes event description, date of onset, clinician's assessment of severity, relationship to IP (assessed only by those with the training and authority to make a diagnosis, or his/her designee), date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to IP.

4.5.2.2. Adverse Events Grading

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to IP (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate DCF and electronic case report form, (eCRF). Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

Severity of Event:

All AEs will be assessed by the clinician using a protocol-defined grading system (refer to protocol Appendix B). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment and generally do not interfere with the participant's daily activities.
- Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

4.5.2.3. Relationship to Study Products:

The clinician's assessment of the AE's relationship to IP will be done by those with the training and authority to make an assessment, or his/her designee, and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study medication must always be suspect. The relationship to study medication will be assessed for AEs using the terms related or not related:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study medication and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study medication caused the event.

4.5.2.4. Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered a SAE if, in the view of either the site PI 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 hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the participant 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.

* Life-threatening adverse event. An AE is considered "life-threatening" if, in the view of either the site PI or sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician or by the Institution as the site PI or Sub Investigator, (SubI).
- Recorded on the appropriate SAE DCF and eCRF.
- Followed through resolution by a licensed study physician.
- Reviewed and evaluated by DMID, an Independent Safety Monitor (ISM) (as deemed necessary), the DSMB (periodic review unless related), and the IRB/IEC.

5. SAMPLE SIZE CONSIDERATIONS

Efficacy analyses will be performed in an evaluable subset of the enrolled population; this subset was used to derive the study's sample size. Assuming a 40% BV recurrence rate among women receiving placebo and a 50% reduction in recurrence among women treated with TOL-463 (i.e. 20% recurrence rate among TOL-463 recipients) and a 1:1 allocation ratio between treatment arms, a sample size of 200 evaluable participants will provide at least 85% power using the Chi-Square Test. Assuming 80% of enrolled participants will be evaluable for the primary analysis, the enrollment target is set to a total of 250 participants to achieve 200 evaluable participants.

The study was closed early due to the uncertain future of the study product's manufacture and availability. It was unrelated to the safety and efficacy of the study product. The power of the actual sample size will be provided in the CSR.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Tabulations will be used extensively to summarize the data. All continuous variables will be summarized using the following descriptive statistics: n (sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the sample size) of observed levels will be reported for all categorical measures. Missing data will be denoted by n and %. Wilson confidence intervals for binomial proportions and difference in binomial proportions will be computed for efficacy variables.

All summary tables will be structured with a column/sub-table for each treatment group (TOL-463 Vaginal Insert, Placebo) and overall (All Subjects), or each site and overall. The total population size relevant to that table/column if applicable, including any missing observations will be displayed in the tables.

Participants will be excluded from Safety Population if it is unknown whether they received at least one dose, so if they had adverse events, those events would not be included in the safety summary tables, but they will be included in the AE listings. Repeat participants are counted once in all TFLs except for the safety analyses, when a participant met safety population criteria in both enrollments, the participant will be counted twice, i.e., each enrollment will be treated distinctly in the safety summary tables.

Data listings will be provided for all data. Note that in the data listings, Subject ID is the unique subject identifier, not the Study ID used on study and dates will not be included, only Study Day.

6.2. Timing of Analyses

The final analysis will be performed after database lock when all subjects have been followed through Visit 4, the final study visit, at Day 85-91.

6.3. Analysis Populations

Safety Population: This analysis population includes all randomized participants who received at least one dose of study treatment. Participants with any evidence of dosing according to the memory aid or study IP packaging return will be included in the Safety population.

Modified Intent-to-Treat (mITT) Population: This analysis population includes all randomized participants who are evaluable (see below). If a participant was enrolled more than once, (participants are allowed to be re-enrolled under PI's discretion for scenarios such as, the first enrollment terminated due to the COVID-19 shelter in place order or became ineligible after enrollment.) only the set of data from the most recent enrollment will be included in the mITT population.

The mITT population will be used as the primary efficacy analysis population.

Per-Protocol (PP) Population: This analysis population includes all randomized participants who are evaluable, complied with the assigned IP (see section 4.4.8), and returned to the study site for the TOC visit within the specified window (Visit 4 [Window: Day 85-91]) or were followed up to their diagnosis of recurrent BV. Participants who violated any inclusion/exclusion criterion at any point during the study or engaged in receptive oral, anal, or vaginal sexual intercourse within 24 hours prior to a study visit will be excluded from the PP population. If a participant was enrolled more than once, (participants are allowed to be re-enrolled under PI's discretion for scenarios such as, the first enrollment terminated due to the COVID-19

shelter in place order or became ineligible after enrollment.) only the set of data from the most recent enrollment will be included in the PP population.

In the unlikely event of an error in randomization or IP administration (i.e., incorrect treatment), participants will be grouped by the treatment they actually received in safety analyses but will be grouped by their intended randomized assignment in efficacy analyses.

Evaluable is defined as follows:

- Negative STI tests taken at baseline (*C. trachomatis*, *N. gonorrhoeae*, or *T. vaginalis*);
- For participants 21 years of age or older, documentation of or self-report of a normal or ASCUS HPV negative Pap test prior to screening, or a Pap smear performed at screening/enrollment with normal result

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

For primary BV recurrence endpoint:

For the mITT analysis population, the BV status of subjects whose status cannot be determined by the TOC visit (visit 4) for any reason will be considered 'treatment failure', including subjects who discontinued early from the study and lack of treatment effect.

For the PP analysis population, subjects whose BV status cannot be determined by the TOC visit for any reason will be excluded from the analysis.

For secondary endpoints, missing values will be further excluded from the mITT and PP populations.

6.6. Interim Analyses and Data Monitoring

The study will be monitored to determine if any of the safety halting rules described in section 8.6 in the protocol are met. The DSMB will meet and review safety data and enrollment data at specified times during the course of study and at a study closeout meeting, as defined in the section 8.7.2 in the protocol and the DSMB Charter.

There are no planned interim efficacy analyses for this study.

Further enrollment will be halted for DSMB review/recommendation if any of the following are reported.

1. If one or more participants experience an SAE judged by an investigator to be related to study IP
2. If two or more participants experience an AE that is judged to be Grade 3 and related to study IP
3. An overall pattern of symptomatic, clinical, or laboratory events that the DMID Medical Monitor or DSMB consider associated with study drug and that may appear minor in terms of individual events, but that may collectively represent a serious potential concern for safety

If any of the halting rules are met, the study will not continue with the remaining enrollments or study treatments without a review by and recommendation from the DSMB to proceed. A summary of halting rules is provided in Table 39**.**

DMID retains the authority to suspend additional enrollment and administration of study product during the entire study, as applicable.

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors participant safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to this study. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will review study progress and participant clinical and safety data at the following time points:

- An initial organizational meeting will be held prior to the study starting and enrollment of participants.
- At specified times during the course of study as defined in the DSMB Charter.
- Ad hoc meeting convened to address a specific safety concern such as when a halting rule is met or for immediate concerns regarding observations during the study.
- A final closeout review will be held within six months after the database is locked to review all cumulative safety data.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with the study administrations (as applicable), and to continue, modify, or terminate the study.

DMID or the DSMB chair may convene the DSMB on an ad hoc basis according to protocol criteria or if there are immediate concerns regarding observations during the course of the study. The DMID Medical Monitor is empowered to stop enrollment and study treatment if AEs that meet the halting criteria are reported. The DMID Medical Monitor and the ISM (as deemed necessary) will be responsible for reviewing SAEs in real time. The DSMB will review SAEs on a regular basis and ad hoc during the study.

6.7. Multicenter Studies

Safety and efficacy data will be pooled across all clinical sites. Center effects are not anticipated because treatment is self-administered, the sites are using standardized procedures for assessment of unsolicited adverse events, and the study relies on a central laboratory for Gram stain Nugent scoring and BD Max. However, as an exploratory analysis, the primary efficacy outcome measure will be tabulated by clinical site (Table 13).

6.8. Multiple Comparisons/Multiplicity

There is only one primary endpoint. No adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Table 2 will present the number of subjects who failed screening and number of subjects that failed to meet each eligibility criterion. Table 3 will present the disposition of subjects overall and by randomized treatment group. Table 4 summarizes the Safety, mITT and PP analysis population eligibilities by treatment group, and reasons excluded. Subjects will be included in the count for a particular reason for exclusion if they met that criterion. As subjects may meet more than one criterion for exclusion, the "Any Reason" counts may be less than the sum of the individual reason counts. Listing 1 provides the subjects excluded from each of the analysis populations and the reasons for exclusion. A listing of subjects who terminated early from the study or discontinued treatment and the reason for early termination or treatment discontinuation will be included in Listing 2 . A listing of subjects who terminated early from the study due to study disruptions from the COVID-19 pandemic will be included in Listing 3.

Figure 2 is a flowchart showing the disposition of study subjects in the safety and efficacy analyses, adapted from the CONSORT statement [7]. It shows the number of subjects eligible, enrolled and randomized, and analyzed for the safety and efficacy analyses, overall and by treatment group.

7.2. Protocol Deviations

Table 5 summarizes subject-specific protocol deviations by deviation category, deviation type, and treatment group for all subjects. All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Listing 4 and Listing 5, respectively.

8. EFFICACY EVALUATION

8.1. Primary Efficacy Analysis

The primary efficacy endpoint for the final analysis is the proportion of subjects with recurrent BV by Test of Cure (TOC, Visit 4 window: Day 85-91) as defined in section 3.3, and in section 6.5 for missing BV status by TOC.

The number of subjects, the proportion of subjects with RBV up to and including V4 will be presented overall and by treatment group with two-sided 95% Wilson confidence interval (no continuity correction). In addition, the difference in proportions between the TOL-463 Vaginal Insert arm and the Placebo group and 95% Newcombe confidence intervals (based on the Wilson CI for the individual proportions) will be presented. See Table 6**.**

The pseudocode to fit the above analyses is below:

```
proc freq data=dataset;

      Table treatment*cure /chisq riskdiff(Newcombe) binomial(wilson) out=output

      alpha=.05;

run;
```

The primary efficacy analysis will be performed in the mITT population (Table 6). As a sensitivity analysis, the primary endpoint will additionally be assessed among all subjects in the mITT population except those terminated early due to study disruptions from the COVID-19 pandemic (Table 7). Analysis of the primary outcome measure will be repeated in the PP analysis population (secondary analysis of primary outcome). See Table 8.

In addition, the rate of recurrence, which considers the amount of observed follow-up time for each participant, will be estimated within each treatment group along with Exact Poisson 95% confidence intervals [8]. We will use a person-time approach as follows. For participants who experience BV recurrence by any visit, the time (in days) of BV recurrence will be defined as the midpoint between the earliest time point of a positive BV diagnosis (post-baseline) and the previous observed time-point. For participants with BV recurrence diagnosed off study, the time (in days) of BV recurrence will be defined as the midpoint between the early termination time point of a positive BV diagnosis off study (post-baseline) and the previous observed time-point. For the participants who did not experience BV recurrence by V4 will contribute the total duration they participated in the study (in days). The participants who withdrew or dropped out early will contribute the number of days they participated in the study. The rate of recurrence = number of recurrence / time each person was observed, totaled for all persons. We will present the estimated recurrence rate in each group and overall, in the mITT population, then repeated in the PP population. See Table 9 and Table 10. The individual time to BV recurrence defined for rate of recurrence is provided in Listing 7.

For efficacy response data, a subject listing of individual Amsel criteria will be provided in Listing 6 for all enrolled subjects, where individual Nugent score will also be included. A summary of Amsel criteria is provided for subjects by visit and treatment group for mITT analysis population in Table 11 and will be repeated in the PP analysis population as a corroborative analysis (Table 12**)**.

As an exploratory analysis, the primary efficacy outcome measure summaries in the mITT population will be tabulated by clinical site (Table 13).

As an ancillary analysis, a summary of Nugent score by visit, category (0-3 normal; 4-6 intermediate; and 7-10 BV) and treatment group for subjects in the mITT population will be presented (Table 14).

8.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be performed in the mITT as the primary population. All the analyses will be repeated in the PP analysis populations as corroborative and sensitivity analyses.

The analysis of Secondary Objective 1, time to BV recurrence will take into account the observed follow-up time for each participant (time-to-event analysis). For this analysis, the outcome will be the time to RBV diagnosis in days from the enrollment visit (day 1). For the participants whose RBV was diagnosed at a scheduled or unscheduled visit, their time of BV recurrence will be defined as the midpoint between the earliest time point of a positive BV diagnosis (post-baseline) and the previous observed time-point. For participants without BV recurrence at or before V4, the BV recurrence endpoint will be coded as censored, with time to recurrence defined as the elapsed time from the first dose of IP, to the earliest of: V4 time-point, the last observed time-point prior to loss to follow-up, or the time- point at which the participant became ineligible for the particular analysis population. Participants with missing time to BV recurrence will be further excluded from analyses in mITT and PP populations, including subjects who had BV recurrence diagnosed off study or subjects who were unknown whether they used any study products. The individual time to BV recurrence defined for secondary objective 1 for mITT and PP populations are also provided in Listing 7.

The null hypothesis for the comparison is that there is no difference in the time to BV recurrence throughout the study between treatment arms, with a two-sided alternative that considers the possibility of a difference in either direction. Kaplan-Meier (KM) curves and associated 95% confidence bands (by treatment groups) will be presented to visually assess the treatment group-specific time-to-recurrence pattern over time. The median time to BV recurrence cannot be calculated because the assumed BV recurrence in the two treatment groups are 20% and 40%. Appropriate quartiles of the time to recurrence will be presented by each treatment group and overall. The KM curves will be presented in Figure 3 for mITT population and in Figure 4 for PP population. The estimate of survival time at which 25% of the subjects have recurrent BV, i.e., 25th percentile of the time to recurrence, by each treatment group and overall will be described in the footnote of the figures.

The pseudocode to fit the above analyses is below:

```
proc lifetest method=KM plots=survival(cb=hw test atrisk) data=dataset outs=surv;

        strata treatment / test=logrank;

      Time time*censor(censored_value);

run;
```

For the Secondary Objective 2, the proportion of participants experiencing vaginal symptoms will be estimated overall, by symptom category, and by treatment group at each visit. See Table 15 for mITT population and Table 16 for PP population. A subject listing of BV symptoms will be presented (Listing 8)

For the Secondary Objective 3, responses to the satisfaction questionnaire will be summarized overall and by treatment group. See Table 17 for mITT population and Table 18 for PP population. Individual subject listings will be presented for all responses to satisfaction questionnaire (Listing 9).

8.3. Exploratory Efficacy Analyses

The exploratory endpoint is to evaluate the performance of the BD Max Vaginal Panel in characterizing clinical and microbiologic outcomes of the intervention. Amsel criteria of 3 or more will be considered as the gold standard for the RBV clinical outcome. Nugent score of ≥7 will be considered as the gold standard for the microbiologic BV outcome. For BD Max Vaginal Panel testing result of BV compared to clinical and microbiologic outcomes, we will present sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and corresponding 95% Wilson CI by study visit (Table 19**)**. The individual BD Max BV result will also be listed in Listing 6.

8.4. Other Analyses

For all enrolled subjects at the screening visit, the original clinical BV diagnosis using Amsel criteria will be compared to the Nugent score assessment in Table 20. Listing 6 will include the individual Amsel criteria assessments and Nugent score at the screening visit.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Demographics and baseline characteristic of the participants will be summarized by clinical sites (Table 21 and Table 23) and treatment groups (Table 22 and Table 24) for all enrolled subjects. Summaries of age, ethnicity, race, and concurrent VVC status at baseline that can be treated by Fluconazole will be presented. Ethnicity is categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race (Multi-Racial) or may refuse to identify a race (Unknown), the latter reflected in the Case Report Form (CRF) as "No" to each racial option. Individual subject listings will be presented for all demographics (Listing 10).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 22.1 or higher. Summaries of subjects' pre-existing medical conditions will be presented by randomized treatment group for all enrolled subjects (Table 25).

An individual subject listing for all enrolled subjects will be presented for all medical conditions (Listing 11).

9.1.2. Prior and Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. Summaries of medications that were started prior to dosing and during follow-up will be presented by WHO Drug Terms 2 and 3 and treatment group (Table 26).

An individual subject listing will be presented for all concomitant medications (Listing 12).

9.1.3. Gynecologic and Sexual History

The number of times the subject had BV in the past 12 months obtained at screening visit will be presented by treatment group and clinical site in the demographics tables (Table 23 and Table 24). Individual subject listings of screening and baseline (Listing 13**)** and follow-up (Listing 14**)** sexual history for all enrolled subjects will be presented**.**

9.2. Measurements of Treatment Compliance

See section 4.4.8. for the definition of treatment compliance that will be used for efficacy analyses. The subject disposition table (Table 3) will present the number and percentage of subject complied with the study treatment by treatment group. Compliance listing will be provided (Listing 15).

9.3. Adverse Events

Safety evaluations will be based on the incidence, severity, and type of AEs, SAEs, clinically significant physical and pelvic examination findings. Safety variables will be tabulated and presented for all participants in the safety population, grouped by type of infection and treatment.

AEs and SAEs will be coded by MedDRA® for preferred term and system organ class. The number of SAEs is likely to be small in this study and will be reported by a detailed listing showing the type, MedDRA®

coding, relevant dates (IP administration dates and AE onset and resolution dates), severity, relatedness, and outcome for each event.

Participants will be excluded from Safety Population if it is unknown whether they received at least one dose, so if they had adverse events, those events would not be included in the safety summary tables or figures, but they will be included in the AE listings. A repeat subject will be re-enrolled under a unique Subject ID and be treated as a distinct subject. If a repeat participant met safety population criteria in both enrollments, the participant will be counted twice, i.e., each enrollment will be treated distinctly in the safety summary tables. All adverse events reported will be documented as unsolicited AEs for this study.

The analyses of Secondary Objective 4 will be conducted in the Safety Population.

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the total safety population size and population within the actual treatment group.

The number of subjects, the proportion of subjects with related AE/SAE, and the 95% Wilson confidence interval for the proportion of subjects who experienced unsolicited AEs/ SAEs related to study product will be presented overall and by treatment group. In addition, the difference in proportions between the TOL-463 Vaginal Insert arm and the Placebo group and 95% Newcomb confidence intervals (based on the Wilson CI for the individual proportions) will be presented. The occurrence of AEs considered product-related following initiation of study treatment and through the final study visit will be presented in Table 27**.**

Table 28 provides an overall summary of AEs and SAEs. Table 29 summarizes all AEs in terms of MedDRA® System Organ Class (SOC), severity, and relationship to study treatment. Table 30 and Table 31 summarizes AEs on the subject level, where a subject is counted once per Preferred Term and is summarized according to their highest severity and closest relationship for the treatment arm and placebo arm respectively. The number and percentage of subjects experiencing unsolicited adverse events with 95% Wilson Confidence Intervals by MedDRA® System Organ Class, and Preferred Term, and Treatment Group will be presented in Table 32. The number of adverse events occurring in 5% of subjects in any treatment group will be presented in Table 33. Figure 5 provides a bar chart of total frequency of adverse events by severity and MedDRA® system organ class. Figure 6 provides a bar chart of total frequency of adverse events by relationship and MedDRA® system organ class. Details of reported AEs are included in Table 34.

9.4. Deaths, Serious Adverse Events and other Significant Adverse Events

A listing of deaths and serious adverse events will be presented including Subject ID, infection type, treatment group, Adverse Event Description, SAE Onset Date, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event in days (Table 35).

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. A listing of the total pregnancies, number of live births, and number of spontaneous abortions, elective abortions or still births will be presented (Listing 16).

9.6. Vital Signs and Physical Evaluations

Vital sign measurements include systolic blood pressure, diastolic blood pressure, and oral temperature, which were no longer collected at any study visits beginning with protocol version 2. Weight and Height were collected at Visit 0/Screening under protocol version 1 or Visit 1/Enrollment beginning with protocol version 2. See Listing 17.

The targeted physical examination data will be summarized by study day, infection type and treatment group for subjects in the Safety population. The following body systems will be assessed: Abdomen; Cardiovascular/heart; Extremities; General Appearance; Head, ears, eyes, nose, and throat; Lymph nodes; Musculoskeletal; Neck; Neurological; Pulmonary/Chest; and Skin (Listing 18).

9.7. Concomitant Medications

Refer to section 9.1.2.

9.8. Pelvic Examination Measures

The analyses of Secondary Objective 5 will be conducted in the Safety Population.

The number of subjects, the proportion of subjects with culture confirmed secondary VVC, and the 95% Wilson confidence interval for the proportion of subjects with culture confirmed secondary VVC following the initiation of the study treatment through the follow-up period will be presented overall and by treatment group. In addition, the difference in proportions between the TOL-463 Vaginal Insert arm and the Placebo group and 95% Newcomb confidence intervals (based on the Wilson CI for the individual proportions) will be presented.

The occurrence of culture confirmed secondary VVC following initiation of study treatment and through the final study visit will be summarized in aggregate and by treatment group will be presented in Table 36 . Table 37 will present the vulvovaginal signs (edema, erythema, and excoriation) and symptoms (itching, burning, and irritation) and a positive KOH microscopy with identification of yeast forms (hyphae/pseudohyphae) or budding yeasts, which clinician's review of clinical diagnosis of VVC will be based on, as well as the culture confirmed VVC. Listing 19 will present the individual culture confirmed VVC and clinically diagnosed VVC data, including data summarized in Table 37 and the yeast forms identified from the yeast culture.

Additional measurements from the pelvic examinations will be summarized and listed. Table 38 presents genital lesion consistent with active HSV or HPV, Motile Trichomonads present on normal saline wet mount microscopy that indicates Trichomonas vaginalis by treatment group and visit. Individual listing of genital lesion consistent with active HSV or HPV, motile trichomonads and additional abnormal pelvic exam findings will be listed in Listing 20.

9.9. Other Laboratory Measures

Listing 21 will present the results of NAAT STI tests (C. trachomatis, N. gonorrhoeae, or T. vaginalis) Pap smear records and test and screening/enrollment for evaluable definition (see section 6.3).

10. PHARMACOKINETICS

Not applicable for this study.

11. IMMUNOGENICITY

Not applicable for this study.

12. OTHER ANALYSES

There are no additional analyses planned for this study.

13. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999". The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. If there are an even number of observations, the median will be reported to one decimal place greater than the original data. If there are an odd number of observations, the median will use the same number of decimal places as the original data. Quantiles other than the median will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

14. TECHNICAL DETAILS

SAS version 9.4 or above will be used to generate all TFL.

15. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The analyses described in this SAP coincide with the analysis descriptions provided in the study protocol.

16. REFERENCES

1. Muzny, C. and J. Schwebke, *Biofilms: an underappreciated mechanism of treatment failure and recurrence in vaginal infections.* Clin Infect Dis, 2015. 61(4): p. 601-606.
2. *Diflucan [package insert]. New York, NY: Pfizer.* 2018.
3. *Nuvessa [package insert]. Irvine, CA: Allergan.* 2016.
4. Marrazzo, J., et al., *Bacterial Vaginosis: Identifying Research Gaps Proceedings of a*Workshop Sponsored by DHHS/NIH/NIAID November 19-20, 2008. Sex Transm Dis, 2010. 37(12): p. 732-744.
5. Aguin, T. and J. Sobel, *Vulvovaginal Candidiasis in Pregnancy*. Curr Infect Dis Rep, 2015. 17(6): p. 462.
6. van de Wijgert, J., et al., *Bacterial vaginosis and vaginal yeast, but not vaginal cleansing, increase HIV-1 acquisition in African women.* J Acquir Immune Defic Syndr, 2008. 48(2): p. 203-210.
7. Drummond R. CONSORT Revised: Improving the Reporting of Randomized Clinical Trials. JAMA. 2001; 285(15):2006-2007.
8. Xinxin G. and Zhaohui S, Confidence Intervals Are a Programmer's Friend. PharmaSUG, 2015. Retrieved from https://www.pharmasug.org/proceedings/2015/SP/PharmaSUG-2015-SP06.pdf

17. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

Table 1: Schedule of Events

Procedures	**Visit 0/V0** Screening (Day -15 to -8)	**Visit 1/V1** Enrollment (Day 1)	**Visit 2/V2** Follow-up (Days 29-35)	**Visit 3/V3** Follow-up (Days 57-63)	**Visit 4/V4/TOC** (Days 85-91)	**Unscheduled Visit**	**Early Termination Visit**
Signed consent form[1]	X	X					
Review of Inclusion/Exclusion criteria	X	X					
Collection of Demographics	X						
Review of Medical History[2, 3]	X	X	X	X	X	(X)	X
Review of Sexual History[4]	X	X	X	X	X	(X)	X
Urine Pregnancy Test[12]	X	X	X	X	X	(X)	X
Review of Concomitant Medications[5]	X	X	X	X	X	(X)	X
Pelvic Examination[3,6, 13]	X	X	X	X	X	(X)	X
Clinical assessment of Vulvovaginal signs	X	X	X	X	X	(X)	X
STI Screen (*C. trachomatis, N. gonorrhoeae*, and *T. vaginalis)*[7]	X						
Clinical Determination of presence or absence of BV (Amsel Criteria)	X	X	X	X	X	(X)	X
Gram stain evaluation/Nugent score for BV	X	X	X	X	X	(X)	X
BD Max Test	X	X	X	X	X		X
Future Analysis Specimen Collection[11]	(X)	(X)	(X)	(X)	(X)		(X)
Dispense Oral Metronidazole (or other CDC-recommended BV treatment)	X						
Randomization		X					
Targeted Physical Examination[8]		X	(X)	(X)	(X)	(X)	(X)
IP Dispensation, Participant Instructions		X	X	X		(X)	
Participant Memory Aid[9]		X	X	X	X	(X)	X
Reminder contact (for Visits 1, 2, and 3)		X	X	X			

Procedures	**Visit 0/V0** Screening (Day -15 to -8)	**Visit 1/V1** Enrollment (Day 1)	**Visit 2/V2** Follow-up (Days 29-35)	**Visit 3/V3** Follow-up (Days 57-63)	**Visit 4/V4/TOC** (Days 85-91)	**Unscheduled Visit**	**Early Termination Visit**
Assessment of IP compliance (via review of Memory Aid and IP return)			X	X	X	(X)	X
Participant Assessment of Vaginal Symptoms	X	X	X	X	X	(X)	X
Candida Culture[10]		(X)	(X)	(X)	(X)	(X)	(X)
Assessment of AEs/SAEs			X	X	X	(X)	X
Participant satisfaction questionnaire			(X)	(X)	X		X

(X) – As indicated/appropriate.

1. At V0 the participant is signing the SIC Form. At V1 the participant will then sign the EIC Form.
2. At V0 collect complete medical symptom history; at subsequent visits, review and update medical symptom history as appropriate.
3. A Pap smear should be done at V0 for any participant who meets the following criteria and cannot provide documentation (which can include self-report) of a normal or ASCUS HPV negative Pap test within the prior 3 years: is 21 years of age or older and (a) has not had a hysterectomy or (b) has had a hysterectomy and has a history of CIN grade 2+ (CIN2+) in the past 20 years. If a Pap smear is conducted at V0, the results are not required prior to enrollment.
4. At V0, collect sexual history for the past 30 days; at subsequent visits, collect interim sexual history since the last visit.
5. At V0, collect concomitant medications taken in the last 30 days; at subsequent visits, collect concomitant medications taken since the last visit.
6. At V1, one pelvic exam is performed and if the participant is enrolled and randomized additional vaginal swabs are collected.
7. Participants who test positive for STIs may be reconsidered for eligibility once the treatment course is complete.
8. At the enrollment visit, V1, this will include weight and height measurements. At all follow-up visits, a targeted physical exam is only performed when clinically indicated.
9. After randomization, the participant will be provided with the Participant Memory Aid for the first 4 weeks of the study. At each of the follow-up visits, V2-V4, the Memory Aid will be reviewed/collected, and a new Memory Aid for the next 4 weeks will be provided.
10. At the enrollment visit, V1, and all follow-up visits V2-V4, participants with clinical evidence of VVC and symptoms will have a confirmatory *Candida* culture performed and treated as appropriate with oral fluconazole.
11. A Future Analysis Specimen Collection is only performed for participants who consented to future use of their specimens.
12. A urine pregnancy test is only required for participants of childbearing potential.
13. The pelvic exam includes KOH and saline microscopy for identification of yeast forms, trichomonas and clue cells.

Table 2: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but Not Enrolled	Any Reason	x	xx
	Time commitment	x	xx
	Concern of risks	x	xx
	Number of procedures	x	xx
	Unable to contact subject	x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

Table 3: Subject Disposition by Treatment Group – All Enrolled Subjects

Subject Disposition	TOL-463 Vaginal Insert (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	N/A	N/A	N/A	N/A	x	N/A
Enrolled/Randomized	x	100	x	100	x	100
Treatment Dispensed	x	xx	x	xx	x	xx
Received Treatment[a]	x	xx	x	xx	x	xx
Received Treatment - Unknown[a]	x	xx	x	xx	x	xx
Completed Follow-up[b]	x	xx	x	xx	x	xx
Complied with Study Treatment throughout Participation[c]	x	xx	x	xx	x	xx
Early Discontinuation from Treatment[d]	x	xx	x	xx	x	xx
Early Termination from Study[b]	x	xx	x	xx	x	xx

[a] Received Treatment includes subjects who successfully received at least one dose of study treatment. It is unknown whether subjects received at least one dose if they were terminated early before Visit 2 and a Study Product Dispensing assessment at the early termination visit could not be conducted.

[b] Completed Follow-up includes subjects who remained BV suppressed and were followed-up through Visit 4 as well as subjects whose participation ended prior to Visit 4 due to a clinical BV diagnosis. Terminated Early includes subjects who terminated from the study early for reasons other than a clinical BV diagnosis.

[c] A blinded case review committee reviewed subjects' data to determine treatment compliance throughout the study for each subject.

[d] Subjects who discontinued treatment due to RBV are included.

Table 4: Analysis Populations by Treatment Group

Analysis Populations	Reason Subjects Excluded	TOL-463 Vaginal Insert (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
Eligible for Safety Analysis Population	N/A	x	xx	x	xx	x	xx
Excluded from Safety Analysis Population	Any Reason	x	xx	x	xx	x	xx
	Did not receive at least one dose of study product	x	xx	x	xx	x	xx
Eligible for Modified Intent-to-Treat Analysis (mITT) Population	N/A	x	xx	x	xx	x	xx
Excluded from for Modified Intent-to-Treat Analysis (mITT) Population	Any Reason	x	xx	x	xx	x	xx
	Positive NAAT test results at baseline for C. trachomatis, N. gonorrhoeae, or T. vaginalis	x	xx	x	xx	x	xx
	HPV Criterion[a]	x	xx	x	xx	x	xx
Eligible for Per-Protocol (PP) Analysis Population	N/A	x	xx	x	xx	x	xx
Excluded from Per-Protocol (PP) Analysis Population	Any Reason	x	xx	x	xx	x	xx
	Did not meet inclusion/exclusion criteria	x	xx	x	xx	x	xx
	Positive NAAT test results at baseline for C. trachomatis, N. gonorrhoeae, or T. vaginalis	x	xx	x	xx	x	xx
	HPV Criterion[a]	x	xx	x	xx	x	xx
	Was not compliant with study product	x	xx	x	xx	x	xx
	Did not return to study site for the TOC visit within the specified window (Visit 4, Day 85-91)	x	xx	x	xx	x	xx
	Was not followed up to the diagnosis of recurrent BV	x	xx	x	xx	x	xx

Notes: N=Number of all enrolled subjects

[a] For participants 21 years of age or older, documentation of or self-report of abnormal, or ASCUS HPV Positive Pap test prior to screening, or Pap smear performed at screening/enrollment with abnormal result.

Table 5: Distribution of Protocol Deviations by Category, Type, and Treatment Group – All Enrolled Subjects

Category	Deviation Type	TOL-463 Vaginal Insert (N=X)		Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type	x	x	x	x	x	x
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion	x	x	x	x	x	x
	ICF not signed prior to study procedures	x	x	x	x	x	x
	Other	x	x	x	x	x	x
Treatment administration schedule	Any type	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x
	Missed treatment administration	x	x	x	x	x	x
	Delayed treatment administration	x	x	x	x	x	x
	Other	x	x	x	x	x	x
Follow-up visit schedule	Any type	x	x	x	x	x	x
	Out of window visit	x	x	x	x	x	x
	Missed visit/visit not conducted	x	x	x	x	x	x
	Other	x	x	x	x	x	x
Protocol procedure/assessment	Any type	x	x	x	x	x	x
	Incorrect version of ICF signed	x	x	x	x	x	x
	Swab not collected	x	x	x	x	x	x
	Urine not collected	x	x	x	x	x	x
	Other specimen not collected	x	x	x	x	x	x
	Specimen result not obtained	x	x	x	x	x	x
	Required procedure not conducted	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x
	Specimen temperature excursion	x	x	x	x	x	x
	Other	x	x	x	x	x	x
Treatment administration	Any type	x	x	x	x	x	x
	Required procedure done incorrectly	x	x	x	x	x	x
	Study product temperature excursion	x	x	x	x	x	x
	Other	x	x	x	x	x	x
Blinding policy/procedure	Any type	x	x	x	x	x	x
	Treatment unblinded	x	x	x	x	x	x
	Other	x	x	x	x	x	x

Note: N=Number of enrolled subjects randomized to the specified treatment group

Table 6: Proportion of Subjects with Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group – mITT Population

Treatment Group	Number of Subjects N	Number of Subjects with RBV n	Proportion of Subjects with RBV	Proportion of Subjects with RBV 95% CI[a]	Difference in Proportions of Subjects with RBV between Treatment Arms	Difference in Proportions of Subjects with RBV between Treatment Arms 95% CI[b]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx		

Notes: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.
[a] 95% Wilson confidence interval for the proportion of subjects with RBV.
[b] 95% Newcombe confidence interval for difference in proportions between arms.

Table 7: Proportion of Subjects with Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group – mITT Population, Excluding Subjects Terminated Early due to COVID-19

Treatment Group	Number of Subjects N[a]	Number of Subjects with RBV n	Proportion of Subjects with RBV	Proportion of Subjects with RBV 95% CI[b]	Difference in Proportions of Subjects with RBV between Treatment Arms	Difference in Proportions of Subjects with RBV between Treatment Arms 95% CI[c]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx		

Notes: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.
[a] This analysis includes all subjects in the mITT population except those terminated early due to study disruptions resulting from shelter in place orders in response to the COVID-19 pandemic.
[b] 95% Wilson confidence interval for the proportion of subjects with RBV.
[c] 95% Newcombe confidence interval for difference in proportions between arms.

Table 8: Proportion of Subjects with Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group – PP Population

Treatment Group	Number of Subjects N	Number of Subjects with RBV n	Proportion of Subjects with RBV	Proportion of Subjects with RBV 95% CI[a]	Difference in Proportions of Subjects with RBV between Treatment Arms	Difference in Proportions of Subjects with RBV between Treatment Arms 95% CI[b]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx		

Notes: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.
[a] 95% Wilson confidence interval for the proportion of subjects with RBV.
[b] 95% Newcombe confidence interval for difference in proportions between arms.

Table 9: Rate of Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group – mITT Population

Treatment Group	Number of Subjects with RBV	Person-days	Rate of RBV	Rate of RBV 95% CI[a]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx

[a] Exact Poisson 95% confidence intervals.

Table 10: Rate of Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group – PP Population

Treatment Group	Number of Subjects with RBV	Person-days	Rate of RBV	Rate of RBV 95% CIa
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx

[a] Exact Poisson 95% confidence intervals.

Table 11: Summary of Amsel Criteria by Study Visit and Treatment group – mITT Population

Amsel Criteria	Subcategories and Summary Statistics	TOL-463 Vaginal Insert (N = xxx)				Placebo (N = xxx)				All Subjects (N = xxx)			
		Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)
Presence of Amsel Criteria	0/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	1/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	2/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	3/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	4/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
pH	>4.5 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Standard Deviation of Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Mean Change from Visit 1	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx
	Standard Deviation of Mean Change from Visit 1	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx
Clue Cells >=20%	Present (%)	x	x	x	x	x	x	x	x	x	x	x	x
Amine ("whiff") test on KOH wet mount	Positive (%)	x	x	x	x	x	x	x	x	x	x	x	x
Homogenous vaginal discharge characteristic of BV	Yes (%)	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the mITT population in the specified group and timepoint.

Data from the previous enrollment(s) of a repeat subject are excluded.

Observations from early termination at an unscheduled visit will be summarized into the preceding scheduled visit. From the scheduled visit and the corresponding unscheduled early termination visit, use the visit with the maximum number of present Amsel criteria for Presence of Amsel Criteria and report each corresponding Amsel criterion from that visit.

Table 12: Summary of Amsel Criteria by Study Visit and Treatment group – PP Population

Amsel Criteria	Subcategories and Summary Statistics	TOL-463 Vaginal Insert (N = xxx)				Placebo (N = xxx)				All Subjects (N = xxx)			
		Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)
Presence of Amsel Criteria	0/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	1/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	2/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	3/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	4/4 (%)	x	x	x	x	x	x	x	x	x	x	x	x
pH	>4.5 (%)	x	x	x	x	x	x	x	x	x	x	x	x
	Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Standard Deviation of Mean	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
	Mean Change from Visit 1	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx
	Standard Deviation of Mean Change from Visit 1	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx	N/A	x.xx	x.xx	x.xx
Clue Cells >=20%	Present (%)	x	x	x	x	x	x	x	x	x	x	x	x
Amine ("whiff") test on KOH wet mount	Positive (%)	x	x	x	x	x	x	x	x	x	x	x	x
Homogenous vaginal discharge characteristic of BV	Yes (%)	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the PP population in the specified group and timepoint.
Data from the previous enrollment(s) of a repeat subject are excluded.

Table 13: Proportion of Subjects with Recurrent Bacterial Vaginosis by the Test of Cure Visit by Treatment Group and by Site – mITT Population

Treatment Group	Number of Subjects N	Number of Subjects with RBV n	Proportion of Subjects with RBV	Proportion of Subjects with RBV 95% CI[a]	Difference in Proportions of Subjects with RBV between Treatment Arms (95% CI[b])
University of Alabama					
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx (0.xx, 0.xx)
Placebo	x	x	0.xx	0.xx, 0.xx	
University of Pittsburgh					
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx (0.xx, 0.xx)
Placebo	x	x	0.xx	0.xx, 0.xx	
University of California					
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx (0.xx, 0.xx)
Placebo	x	x	0.xx	0.xx, 0.xx	

Notes: The denominator for proportions is based on the number of subjects enrolled in the respective treatment group.
[a] 95% Wilson confidence interval for the proportion of subjects with RBV.
[b] 95% Newcombe confidence interval for difference in proportions between arms.

Table 14: Nugent Scores by Category, Study Visit, and Treatment Group - mITT Population

Nugent Score Category	TOL-463 Vaginal Insert (N = xxx)				Placebo (N = xxx)				All Subjects (N = xxx)			
	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)	Visit 1 (N = xxx)	Visit 2 (N = xxx)	Visit 3 (N = xxx)	Visit 4 (N = xxx)
0-3 (Normal) (%)	x	x	x	x	x	x	x	x	x	x	x	x
4-6 (Intermediate) (%)	x	x	x	x	x	x	x	x	x	x	x	x
7-10 (BV) (%)	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the mITT population in the specified group. Data shown in this table are percentages, where N is the denominator.

Table 15: Summary of Proportion of Participants Reporting BV Symptoms – mITT Population

Symptoms and Signs	Symptoms Subcategories	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Abnormal Vaginal Discharge	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, consistent with BV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vaginal Odor	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, consistent with BV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the mITT population in the specified group.
Subjects will be further excluded if no data is available at the specified timepoint, n=Number of subjects with available data for the specified category at the specified timepoint, and these counts are shown in the row of n, whereas the data shown in the rows of each response level in this table are percentages, where n is the denominator.
For post-enrollment visits, observations from early termination at an unscheduled visit will be summarized into the preceding scheduled visit. For Vaginal Discharge and Odor responses from the scheduled visit and the corresponding unscheduled early termination visit, count the subject in "Yes, consistent with BV" when at least one response was "Yes, consistent with BV"; count the subject in "Yes, other" when no response was in "Yes, consistent with BV" and at least one response was from "Yes, other"; count the subject in "No" when all responses were "No".

Table 16: Summary of Proportion of Participants Reporting BV Symptoms – PP Population

Symptoms and Signs	Subcategories	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Abnormal Vaginal Discharge	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, consistent with BV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vaginal Odor	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
	No	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, consistent with BV	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Yes, other	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the PP population in the specified group.
Subjects will be further excluded if no data is available at the specified timepoint, n=Number of subjects with available data for the specified category at the specified timepoint.
Data shown in this table are percentages, where n is the denominator.

Table 17: Summary of Responses to the Satisfaction Questionnaire – mITT Population

Satisfaction Questions	Responses	TOL-463 Vaginal Insert (N=X)	Placebo (N=X)	All Subjects (N=X)
How Easy to Use	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
How Often to Use	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
How Convenient to Use	n	n	n	n
	Extremely inconvenient	x	x	x
	Very inconvenient	x	x	x
	Inconvenient	x	x	x
	Somewhat convenient	x	x	x
	Convenient	x	x	x
	Very convenient	x	x	x

Satisfaction Questions	Responses	TOL-463 Vaginal Insert (N=X)	Placebo (N=X)	All Subjects (N=X)
	Extremely convenient	x	x	x
Overall Satisfaction	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
Would Use Again	n	n	n	n
	Yes	x	x	x

Notes: N=Number of subjects in the mITT population in the specified group.
Subjects will be further excluded if no data is available, n=Number of subjects with available data for the specified question, and these counts are shown in the row of n, whereas the data shown in the rows of each response level in this table are percentages, where n is the denominator.
The questions are structured as "How satisfied or dissatisfied are you with …", where the following part of the question is shown in the table.

Table 18: Summary of Responses to the Satisfaction Questionnaire – PP Population

Satisfaction Questions	Responses	TOL-463 Vaginal Insert (N=X)	Placebo (N=X)	All Subjects (N=X)
How Easy to Use	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
How Often to Use	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
How Convenient to Use	n	n	n	n
	Extremely inconvenient	x	x	x
	Very inconvenient	x	x	x
	Inconvenient	x	x	x
	Somewhat convenient	x	x	x
	Convenient	x	x	x
	Very convenient	x	x	x

Satisfaction Questions	Responses	TOL-463 Vaginal Insert (N=X)	Placebo (N=X)	All Subjects (N=X)
	Extremely convenient	x	x	x
Overall Satisfaction	n	n	n	n
	Extremely dissatisfied	x	x	x
	Very dissatisfied	x	x	x
	Dissatisfied	x	x	x
	Somewhat satisfied	x	x	x
	Satisfied	x	x	x
	Very satisfied	x	x	x
	Extremely satisfied	x	x	x
Would Use Again	n	n	n	n
	Yes	x	x	x

Notes: N=Number of subjects in the PP population in the specified group.
Subjects will be further excluded if no data is available, n=Number of subjects with available data for the specified question, and these counts are shown in the row of n, whereas the data shown in the rows of each response level in this table are percentages, where n is the denominator.
The questions are structured as "How satisfied or dissatisfied are you with …", where the following part of the question is shown in the table.

Table 19: Performance of BD Max Vaginal Panel

Study Visit	Condition	N	Prevalence	BD Max Proportion of Positives	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV[a] (%) (95% CI)	NPV[b] (%) (95% CI)
Visit 1 - Enrollment	Clinical BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
	Microbiological BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
Visit 2 – Month 2	Clinical BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
	Microbiological BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
Visit 3 – Month 3	Clinical BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
	Microbiological BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
Visit 4 – Month 4	Clinical BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)
	Microbiological BV	x	0.xx	0.xx	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)	x (0.xx, 0.xx)

Notes: N is number of subjects with available BV results from both the standard diagnosis method (clinical diagnosis or microbiological diagnosis as specified by the row) and the BD Max Vaginal Panel testing method.
95% CI Wilson confidence interval is provided in this table.
[a] Positive Predictive Value
[b] Negative Predictive Value

Table 20: Original Clinical BV Diagnosis and the Nugent Score Assessment at the Screening Visit - All Enrolled Subjects

BV Diagnosis Methods	Subcategories and Summary Statistics	TOL-463 Vaginal Insert (N = xxx)	Placebo (N = xxx)	All Subjects (N = xxx)
Nugent Score Category	0-3 (Normal) (%)	x	x	x
	4-6 (Intermediate) (%)	x	x	x
	7-10 (BV) (%)	x	x	x
Presence of Amsel Criteria	0/4 (%)	x	x	x
	1/4 (%)	x	x	x
	2/4 (%)	x	x	x
	3/4 (%)	x	x	x
	4/4 (%)	x	x	x
pH	>4.5 (%)	x	x	x
	Mean	x	x	x
	Standard Deviation of Mean	x	x	x
Clue Cells >=20%	Present (%)	x	x	x
Amine ("whiff") test on KOH wet mount	Positive (%)	x	x	x
Homogenous vaginal discharge characteristic of BV	Yes (%)	x	x	x

Notes: N=Number of enrolled subjects in the specified group.
For percentages shown in this table, N is the denominator.

Table 21: Summary of Categorical Demographic and Baseline Characteristics by Site - All Enrolled Subjects

Variable	Characteristic	University of Alabama (N=X)		University of Pittsburgh (N=X)		University of California (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Sex	Female	x	x	x	x	x	x	x	xx
Ethnicity	Hispanic or Latino	x	x	x	x	x	x	x	xx
	Not Hispanic or Latino	x	x	x	x	x	x	x	xx
	Not Reported	x	x	x	x	x	x	x	xx
	Unknown	x	x	x	x	x	x	x	xx
Race	American Indian or Alaskan Native	x	x	x	x	x	x	x	xx
	Asian	x	x	x	x	x	x	x	xx
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	x	x	xx
	Black or African American	x	x	x	x	x	x	x	xx
	White	x	x	x	x	x	x	x	xx
	Multi-Racial	x	x	x	x	x	x	x	xx
	Unknown	x	x	x	x	x	x	x	xx
Concurrent VVC Status[a]	Positive	x	x	x	x	x	x	x	xx
	Negative	x	x	x	x	x	x	x	xx

Notes: N=Number of enrolled subjects in the specified group. Data from the previous enrollment(s) of a repeat subject are excluded.
[a] Culture confirmed Vulvovaginal Candidiasis at baseline.

Table 22: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Characteristic	TOL-463 (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	n	n	n	n	%
Sex	Female	x	x	x	x	x	xx
Ethnicity	Not Hispanic or Latino	x	x	x	x	x	xx
	Hispanic or Latino	x	x	x	x	x	xx
	Not Reported	x	x	x	x	x	xx
	Unknown	x	x	x	x	x	xx
Race	American Indian or Alaskan Native	x	x	x	x	x	xx
	Asian	x	x	x	x	x	xx
	Native Hawaiian or Other Pacific Islander	x	x	x	x	x	xx
	Black or African American	x	x	x	x	x	xx
	White	x	x	x	x	x	xx
	Multi-Racial	x	x	x	x	x	xx
	Unknown	x	x	x	x	x	xx
Concurrent VVC Status[a]	Positive	x	x	x	x	x	xx
	Negative	x	x	x	x	x	xx

Notes: N=Number of enrolled subjects in the specified group. Data from the previous enrollment(s) of a repeat subject are excluded.
[a] Culture confirmed Vulvovaginal Candidiasis at baseline.

Table 23: Summary of Continuous Demographic and Baseline Characteristics by Site - All Enrolled Subjects

Variable	Statistic	University of Alabama (N=X)	University of Pittsburgh (N=X)	University of California (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	x	x	x	x
	Minimum	x	x	x	x
	Maximum	x	x	x	x
No. of Times Subject Had BV in the Past 12 Months Obtained at Screening Visit	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	x	x	x	x
	Minimum	x	x	x	x
	Maximum	x	x	x	x

Notes: N=Number of enrolled subjects in the specified group. Data from the previous enrollment(s) of a repeat subject are excluded.

Table 24: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Statistic	TOL-463 (N=X)	Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
No. of Times Subject Had BV in the Past 12 Months Obtained at Screening Visit	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x

Notes: N=Number of enrolled subjects in the specified group. Data from the previous enrollment(s) of a repeat subject are excluded.

Table 25: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group – All Enrolled Subjects

MedDRA System Organ Class	TOL-463 Vaginal Insert (N=X)		Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]	x	xx	x	xx	x	xx
[SOC 2]	x	xx	x	xx	x	xx

Notes: N= Number of enrolled subjects in the specified group; n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

Table 26: Number and Percentage of Subjects with Prior and Concomitant Medications by WHO Drug Classification and Treatment Group – Safety Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	TOL-463 Vaginal Insert (N=X)		Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x	xx	x	xx	x	xx
	[ATC 2 - 1]	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx
[ATC Level 1 – 2]	[ATC 2 - 1]	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx

N = Number of subjects in the Safety Population. n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Table 27: Occurrence of Related Adverse Events (AE) Overall and by Treatment Groups – Safety Population

Treatment Group	Number of Subjects N	Number of Subjects with Related AE n	Proportion of Subjects with Related AE	Proportion of Subjects with Related AE 95% CI[a]	Difference in Proportions of Subjects with Related AE between Treatment Arms	Difference in Proportions of Subjects with Related AE between Treatment Arms 95% CI[b]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx		

Notes: The denominator for proportions is based on the number of subjects who used at least one insert in the respective treatment group.
[a] 95% Wilson confidence interval for the proportion of subjects with Related AE.
[b] 95% Newcombe confidence interval for difference in proportions between arms.

Table 28: Overall Summary of Adverse Events – Safety Population

	TOL-463 Vaginal Insert (N = xx)		Placebo (N = xx)		All Subjects (N = xx)	
Subjects[a] with	n	%	n	%	n	%
At least one unsolicited adverse event	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x
At least one serious adverse event	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x

Notes: Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings. A repeat subject will be re-enrolled under a unique Subject ID and be treated as a distinct subject in this table.

N = Number of subjects in the Safety Population

[a] Subjects are counted once for each category regardless of the number of events.

[b] A listing of Serious Adverse Events is included in Table 34 .

[c] As reported on the Adverse Event eCRF.

Table 29: Unsolicited Adverse Events Cross-Classified by MedDRA System Organ Class and Preferred Term, Severity, and Relationship to Study Treatment - Safety Population

MedDRA System Organ Class	Preferred Term	Severity	TOL-463 Vaginal Insert (N = xx)			Placebo (N = xx)			All Subjects (N = xx)		
			Related	Not Related	Total	Related	Not Related	Total	Related	Not Related	Total
			n	n	n	n	n	n	n	n	n
Any SOC	Any PT	Any Severity	x	x	x	x	x	x	x	x	x
		Mild	x	x	x	x	x	x	x	x	x
		Moderate	x	x	x	x	x	x	x	x	x
		Severe	x	x	x	x	x	x	x	x	x
SOC 1	PT 1	Any Severity	x	x	x	x	x	x	x	x	x
		Mild	x	x	x	x	x	x	x	x	x
		Moderate	x	x	x	x	x	x	x	x	x
		Severe	x	x	x	x	x	x	x	x	x
	PT 2	Any Severity	x	x	x	x	x	x	x	x	x
		Mild	x	x	x	x	x	x	x	x	x
		Moderate	x	x	x	x	x	x	x	x	x
		Severe	x	x	x	x	x	x	x	x	x

Notes: N= Number of subjects in the Safety population. Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings. A repeat subject will be re-enrolled under a unique Subject ID and be treated as a distinct subject in this table.

Table 30: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, and Relationship – TOL-463 Vaginal Insert Group - Safety Population

[Implementation note: Do not show "however, a subject will be counted once again under the "Not Yet Determined" column if they have events that fall under this category." in the footnote if such scenario doesn't exist.]

				Severity						Relationship to Treatment			
		Any Incidence		Mild		Moderate		Severe		Not Related		Related	
MedDRA System Organ Class	MedDRA Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 2]	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 2]	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 2]	x	x	x	x	x	x	x	x	x	x	x	x

Notes: A subject is only counted once per PT and is summarized according to their highest severity and closest relationship, however, a subject will be counted once again under the "Not Yet Determined" column if they have events that fall under this category.
Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings.
A repeat subject will be re-enrolled under a unique Subject ID and be treated as a distinct subject in this table.

Table 31: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Severity, and Relationship – Placebo Group - Safety Population

[Implementation note: Do not show "however, a subject will be counted once again under the "Not Yet Determined" column if they have events that fall under this category." in the footnote if such scenario doesn't exist.]

				Severity						Relationship to Treatment			
		Any Incidence		Mild		Moderate		Severe		Not Related		Related	
MedDRA System Organ Class	MedDRA Preferred Term	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 1]	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 2]	x	x	x	x	x	x	x	x	x	x	x	x
[SOC 2]	Any PT	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 1]	x	x	x	x	x	x	x	x	x	x	x	x
	[PT 2]	x	x	x	x	x	x	x	x	x	x	x	x

Notes: A subject is only counted once per PT and is summarized according to their highest severity and closest relationship, however, a subject will be counted once again under the "Not Yet Determined" column if they have events that fall under this category.
Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings.
A repeat subject will be re-enrolled under a unique Subject ID and be treated as a distinct subject in this table.

Table 32: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class, and Preferred Term, and Treatment Group

MedDRA® System Organ Class	MedDRA® Preferred Term	TOL-463 Vaginal Insert (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any SOC	Any PT	x	x	x, x	x	x	x, x	x	x	x, x
[SOC 1]	Any PT	x	x	x, x	x	x	x, x	x	x	x, x
	[PT 1]	x	x	x, x	x	x	x, x	x	x	x, x
	[PT 2]	x	x	x, x	x	x	x, x	x	x	x, x
[SOC 2]	Any PT	x	x	x, x	x	x	x, x	x	x	x, x
	[PT 1]	x	x	x, x	x	x	x, x	x	x	x, x
	[PT 2]	x	x	x, x	x	x	x, x	x	x	x, x

Notes: N = number of subjects in the Safety Analysis Population who received the specified dose.
This table presents number and percentage of subjects.
A subject is only counted once per PT/timepoint.
95% Wilson CI is provided.

Table 33: Unsolicited Adverse Events Occurring in 5% of Subjects in Any Treatment Group by MedDRA System Organ Class and Preferred Term, and Treatment Group - Safety Population

Preferred Term	MedDRA System Organ Class	TOL-463 Vaginal Insert (N=X)			Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc.	Etc.	x	x	x	x	x	x	x	x	x
Other (Non-serious) Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
PT1	SOC1	x	x	x	x	x	x	x	x	x
Etc	Etc	x	x	x	x	x	x	x	x	x

N = number of subjects in the Safety Population (number of subjects at risk).
n= number of subjects reporting event.
Events= total frequency of events reported.

Table 34: Listing of Non-Serious, Unsolicited Adverse Events – All Enrolled Subjects

[Implementation notes: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Treatment Group, Subject ID, AE Number.

Show footnote if the following scenario exist: Notes: Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings.]

Adverse Event	No. of Days Post First Dose	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:										
Comments:										
Treatment Group: , Subject ID: , AE Number:										
Comments:										

Table 35: Listing of Serious Adverse Events – All Enrolled Subjects

[Implementation notes: If the event is ongoing (no stop date), indicate "ongoing" in the "Duration" column. In the "If Not Related, Alternate Etiology" column, merge the 2 data fields for collecting alternate etiology, separate by a colon. If there are no comments for an event, populate 'Comments' row with 'None'. In the CSR, Subject ID should be USUBJID (not PATID) for purposes of de-identification. Listing should be sorted by Treatment Group, Subject ID, AE Number.

Show footnote if the following scenario exist: Notes: Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings]

Adverse Event	No. of Days Post First Dose	Duration (Days)	Reason Reported as an SAE	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											

Table 36: Occurrence of Culture Confirmed Secondary Vulvovaginal Candidiasis (VVC) Overall and by Treatment Groups – Safety Population

Treatment Group	Number of Subjects N	Number of Subjects with VVC[a] n	Proportion of Subjects with VVC	Proportion of Subjects with VVC 95% CI[b]	Difference in Proportion of Subjects with VVC between Treatment Arms	Difference in Proportion of Subjects with VVC between Treatment Arms 95% CI[c]
TOL-463 Vaginal Insert	x	x	0.xx	0.xx, 0.xx	0.xx	0.xx, 0.xx
Placebo	x	x	0.xx	0.xx, 0.xx		

Notes: The denominator for proportions is based on the number of subjects who used at least one insert in the respective treatment group.
[a] The occurrence of culture confirmed secondary VVC following initiation of study treatment and through the final study visit is calculated. Subjects enrolled with concurrent VVC at baseline (visit 1) that can be treated with oral fluconazole is not counted towards n.
[b] 95% Wilson confidence interval for the proportion of subjects with VVC.
[c] 95% Newcombe confidence interval for difference in proportions between arms.

Table 37: Summary of Proportion of Participants Reporting Vulvovaginal Symptoms and Signs, Yeast Form, and Clinical Diagnosed and Culture Confirmed Vulvovaginal Candidiasis – Safety Population

	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
Symptoms/Signs Severity	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Burning															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
None	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Irritation															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
None	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Itching															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
None	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Edema															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
Symptoms/Signs Severity	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Erythema															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Excoriation															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Mild	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Moderate	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Severe	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
KOH Wet Mount Microscopy: Yeast (budding, branching, hyphae)															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Present	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical Diagnosis of Vulvovaginal Candidiasis															
n	N/A	n	n	n	n	N/A	n	n	n	n	N/A	n	n	n	n
Yes	N/A	x	x	x	x	N/A	x	x	x	x	N/A	x	x	x	x
No	N/A	x	x	x	x	N/A	x	x	x	x	N/A	x	x	x	x
Culture Confirmed Vulvovaginal Candidiasis															
n	N/A	n	n	n	n	N/A	n	n	n	n	N/A	n	n	n	n
Yes	N/A	x	x	x	x	N/A	x	x	x	x	N/A	x	x	x	x
No	N/A	x	x	x	x	N/A	x	x	x	x	N/A	x	x	x	x

	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
Symptoms/Signs Severity	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**

Notes: N=Number of subjects in the Safety population in the specified group.
Subjects will be further excluded if no data is available at the specified timepoint, n=Number of subjects with available data for the specified category at the specified timepoint, and these counts are shown in the row of n, whereas the data shown in the rows of each response level in this table are percentages, where n is the denominator.
Observations from early termination at an unscheduled visit will be summarized into the preceding scheduled visit. For Burning, Irritation, Itching, Edema, Erythema, and Excoriation, the maximum severity level from the scheduled visit and the corresponding unscheduled early termination visit will be counted. For KOH wet mount Microcopy responses from the scheduled visit and the corresponding unscheduled early termination visit, count the subject in "Present" when at least one response was "Present", and count "Absent" when all responses were "Absent".

Table 38: Additional Pelvic Examination Measures

Measures	TOL-463 Vaginal Insert (N=X)					Placebo (N=X)					All Subjects (N=X)				
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Genital lesion consistent with active HSV or HPV:															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Present	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Motile Trichomonads															
n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Absent	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Present	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Notes: N=Number of subjects in the Safety population in the specified group.
Subjects will be further excluded if no data is available at the specified timepoint, n=Number of subjects with available data for the specified category at the specified timepoint, and these counts are shown in the row of n, whereas the data shown in the rows of each response level in this table are percentages, where n is the denominator.
Observations from early termination at an unscheduled visit will be summarized into the preceding scheduled visit. For responses from the scheduled visit and the corresponding unscheduled early termination visit, count the subject in "Present" when at least one response was "Present", and count "Absent" when all responses were "Absent".

Table 39: Summary of Halting Rules – Safety Population

Halting Rule #	Rule	Halting Rule Triggered (Yes/No)	# Contributing to Halting Rule/ Total Needed to Halt
1	If one or more participants experience an SAE judged by an investigator to be related to study IP	Yes/No	x/1
2	If two or more participants experience an AE that is judged to be Grade 3 and related to study IP	Yes/No	x/2
3	An overall pattern of symptomatic, clinical, or laboratory events that the DMID Medical Monitor or DSMB consider associated with study drug and that may appear minor in terms of individual events, but that may collectively represent a serious potential concern for safety.	Yes/No	0

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

Figure 2: CONSORT Flow Diagram

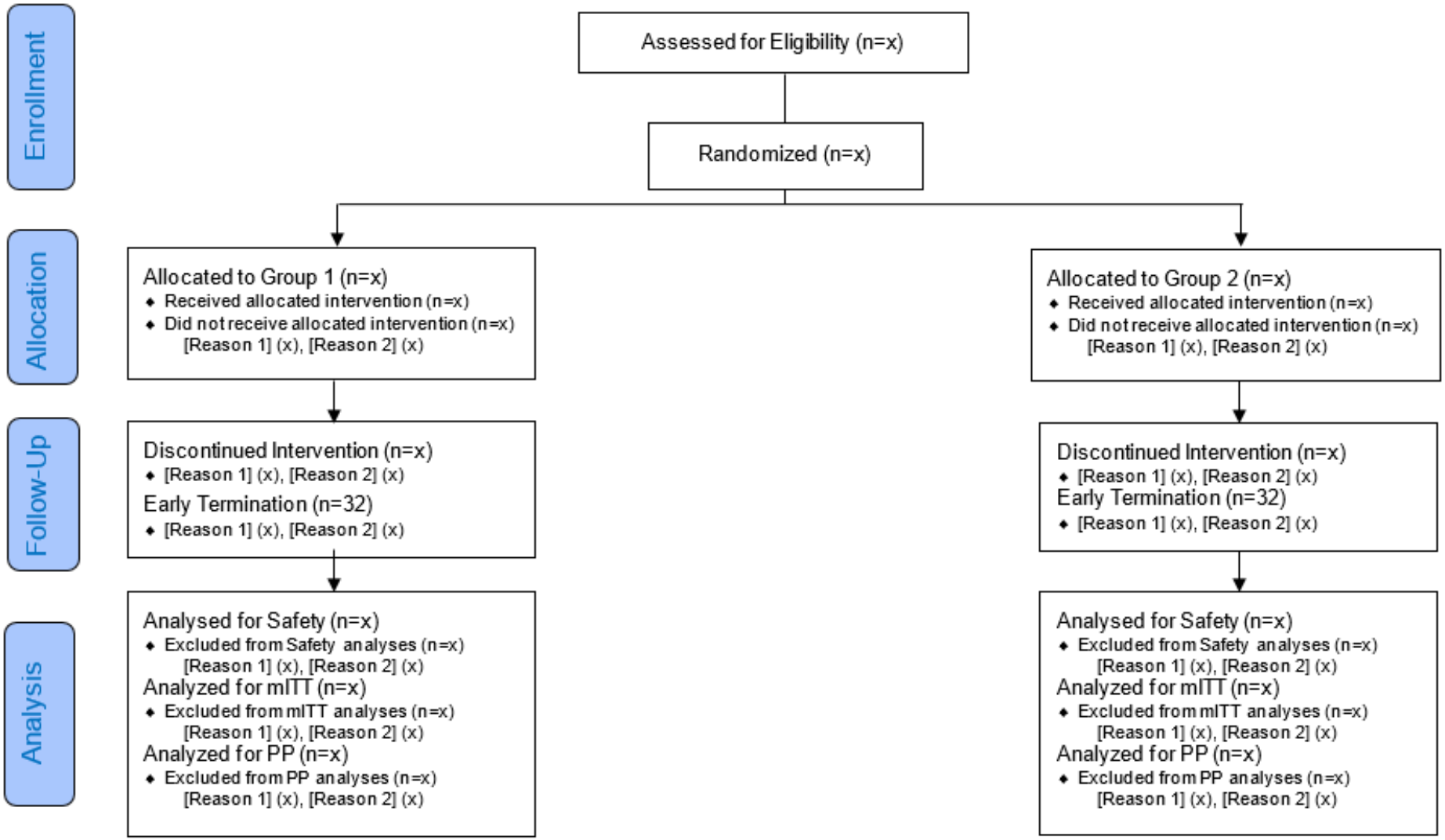
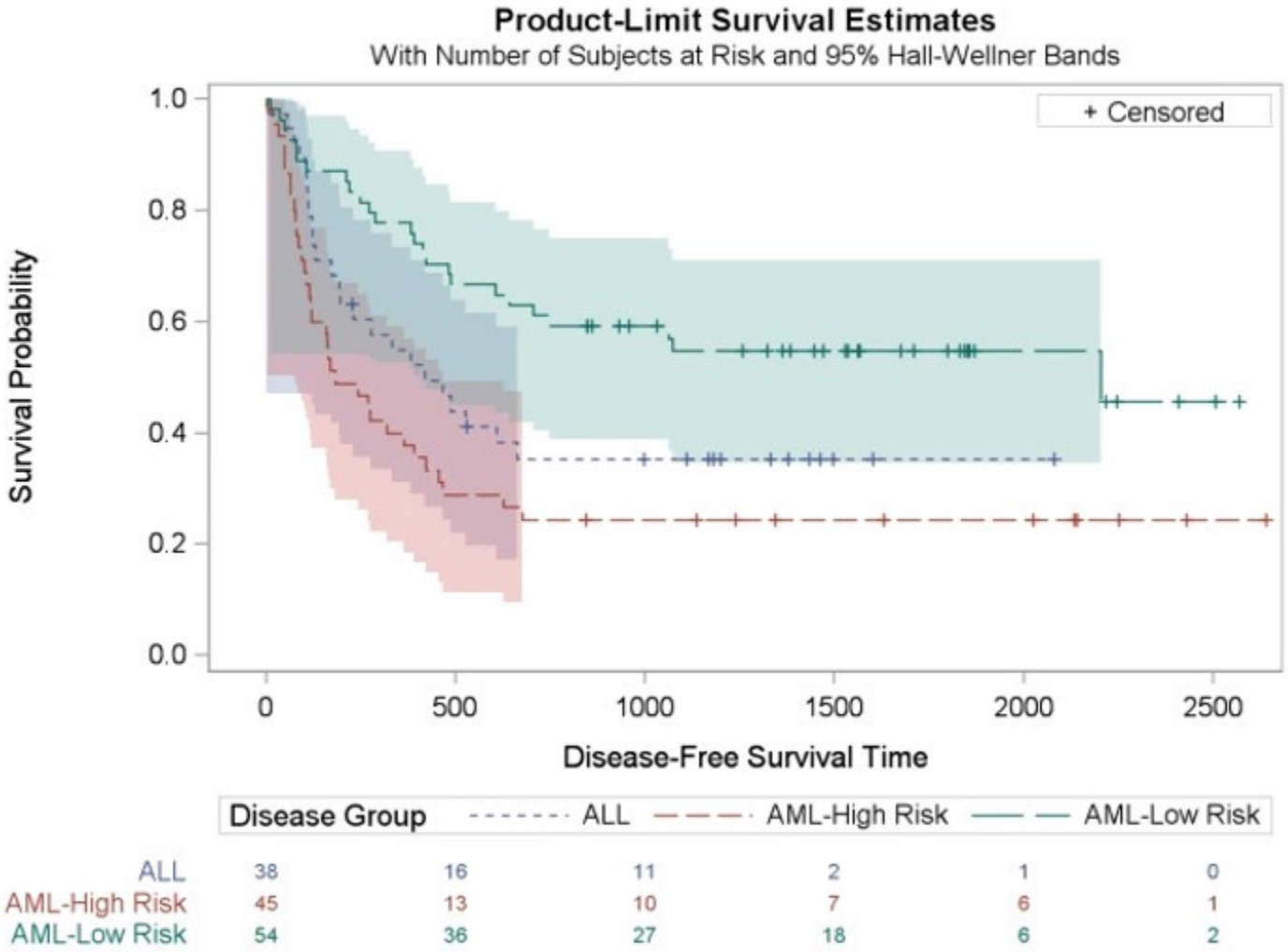


Figure 3: Time to Bacterial Vaginosis Recurrence - mITT population

[Implementation notes: 3 curves are for overall and each treatment group. X-axis label: Time (Days) to Bacterial Vaginosis Recurrence, x-axis label: Proportion of Survival.

Display, number of subjects at risk table with ticks at day 0, 15, 30, 45, 60, 75, 90 on x-axis, and 95% HW confidence bands of the curves in the plot. Legend names: Treatment arm, All, TOL-463 Vaginal Insert, Placebo. Obtain the estimates in the footnote from the SAS proc lifetest Quartile Estimates output table.]

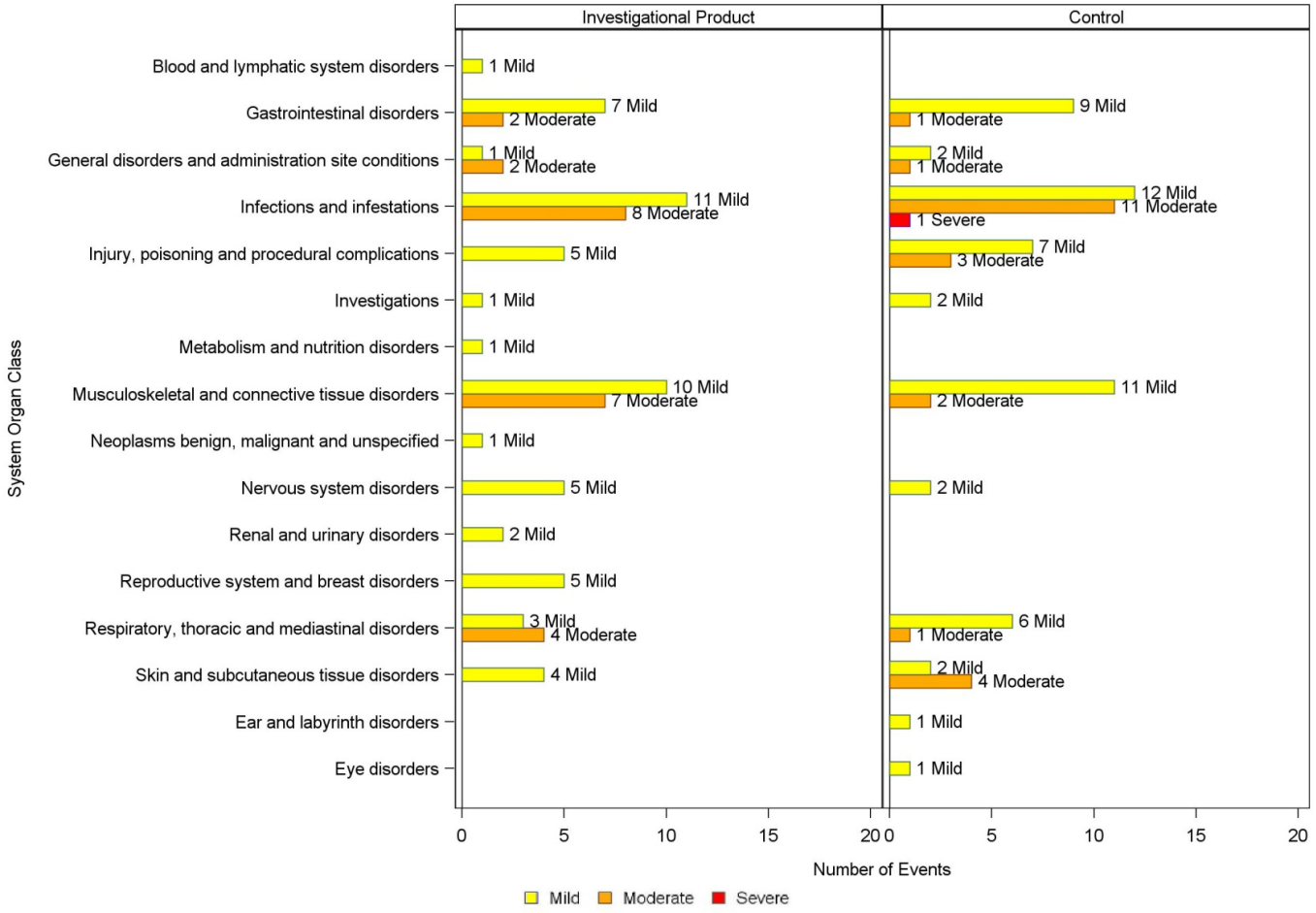


Notes: The estimate of survival time at which 25% of the overall subjects are expected to have recurrent BV (Proportion of survival equals to 0.75 at y-axis) is X days (95% CI: X - X), and correspondingly, X days (95% CI: X - X) for the TOL-463 group and X days (95% CI: X - X) for the Placebo group.

Figure with similar format:

Figure 4: Time to Bacterial Vaginosis Recurrence - PP population

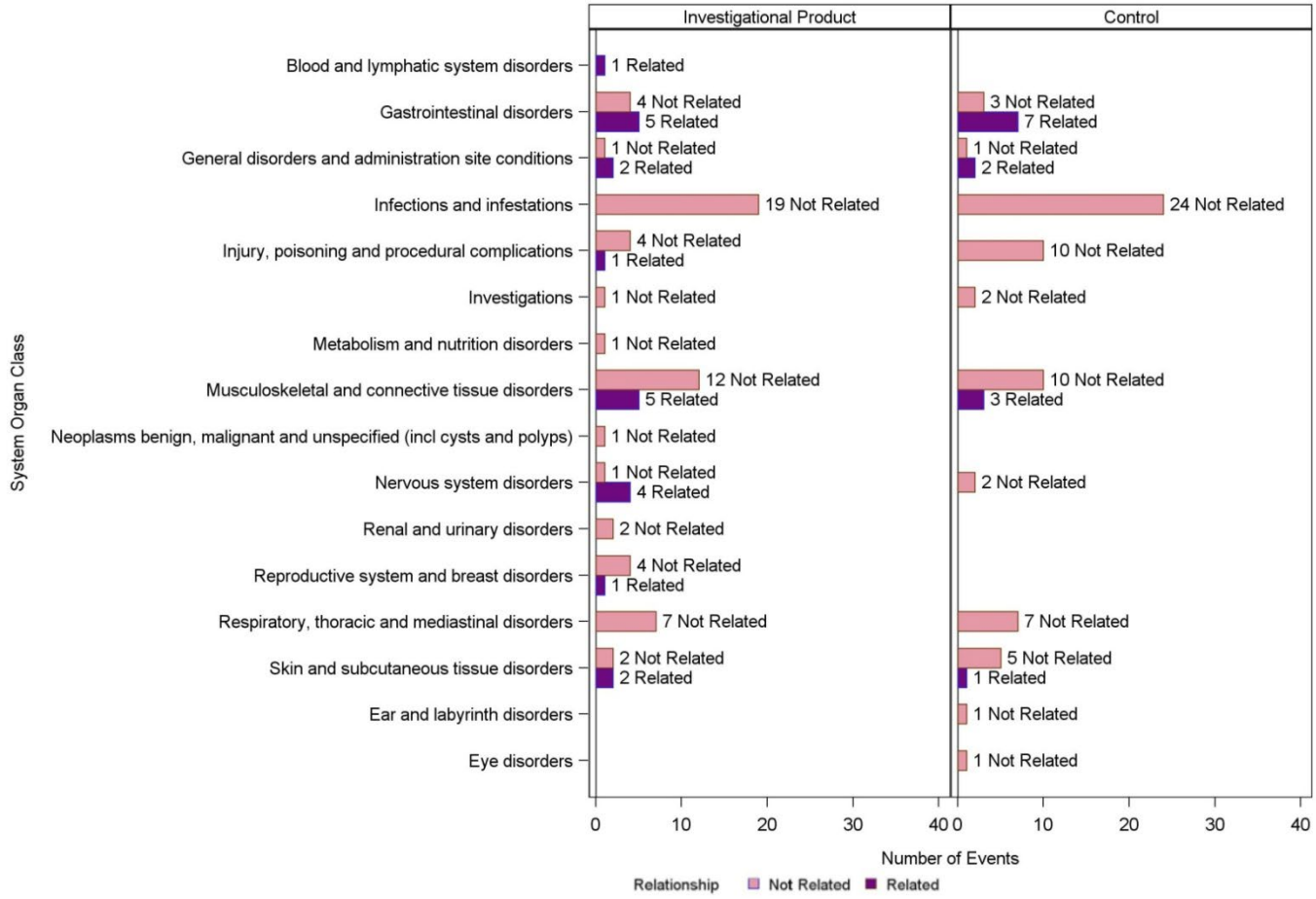
Figure 5: Number and Severity of Unsolicited Adverse Events by MedDRA System Organ Class - Safety Population



Figures will have 3 panels: TOL-463 Vaginal Insert, Placebo, All Subjects

Show footnote if the following scenario exist: Notes: Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings

Figure 6: Number of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship - Safety Population



Figures will have 3 panels: TOL-463 Vaginal Insert, Placebo, All Subjects

Show footnote if the following scenario exist: Notes: Subjects are excluded from Safety Population if it is unknown whether they received at least one dose, but the adverse events of such subjects are included in the AE listings

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
TOL-463 Vaginal Insert/Placebo	xxxxxx	[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]	Yes/No	xxxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxx	[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]	Yes/No	xxxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxx	[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]	Yes/No	xxxxxx

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

Listing 2: Early Terminations or Discontinued Subjects

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Category.
2. Category will be "Early Termination" or "Treatment Discontinuation". If a subject discontinued treatment, they will have two records.
3. In the “Reason” column, concatenate any “specify” fields, including AE number and DV number.

Treatment Group	Subject ID	Site	Category	Reason for Early Termination or Treatment Discontinuation	Study Day Corresponding to Early Termination/Treatment Discontinuation	Last Completed Study Visit Prior to Termination
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/ Treatment Discontinuation	xxxxxxxx	xx	Visit x
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/Treatment Discontinuation	xxxxxxxx	xx	Visit x
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/Treatment Discontinuation	xxxxxxxx	xx	Visit x

Notes: Subjects listed do not include those terminated early due to study disruptions resulting from the COVID-19 pandemic. See Listing 3 for a complete listing of early terminations due to COVID-19 shelter in place orders.

Listing 3: Subjects Terminated Early due to the COVID-19 Pandemic

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Category.
2. Category will be "Early Termination" or "Treatment Discontinuation". If a subject discontinued treatment, they will have two records.
3. In the “Reason” column, concatenate any “specify” fields, including AE number and DV number.

Treatment Group	Subject ID	Site	Category	Reason for Early Termination or Treatment Discontinuation	Study Day Corresponding to Early Termination/Treatment Discontinuation	Last Completed Study Visit Prior to Termination
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/ Treatment Discontinuation	xxxxxxxx	xx	Visit x
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/Treatment Discontinuation	xxxxxxxx	xx	Visit x
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	Early Termination/Treatment Discontinuation	xxxxxxxx	xx	Visit x

Notes: Subjects listed were terminated early due to study disruptions resulting from shelter in place orders in response to the COVID-19 pandemic.

Listing 4: Subject-Specific Protocol Deviations

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Deviation Number.
2. In the Deviation Description column concatenate any specify fields.
3. In the Reason for Deviation column concatenate any specify fields.

Treatment Group	Subject ID	DV Number	Deviation Description	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments
TOL-463 Vaginal Insert /Placebo	xxxxxx	xx	xxxxxxxx	xxxxxxxx	xx	xxxxxxxx	Yes/No	Yes/No	Yes/No	Yes/No	xxxxxxxx
TOL-463 Vaginal Insert /Placebo	xxxxxx	xx	xxxxxxxx	xxxxxxxx	xx	xxxxxxxx	Yes/No	Yes/No	Yes/No	Yes/No	xxxxxxxx

Listing 5: Non-Subject-Specific Protocol Deviations

Implementation Notes:

1. Sort order will be by Site, Start Day.
2. In the Deviation Description column concatenate any specify fields.
3. In the Reason for Deviation column concatenate any specify fields.

Site	Start Date	Deviation Description	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments
xxxx	ddMMMyyyy	xxxx	ddMMMyyyy	xxxx	Yes/No	Yes/No	xx	xxxx	xxxxxxxx
xxxx	ddMMMyyyy	xxxx	ddMMMyyyy	xxxx	Yes/No	Yes/No	xx	Xxxx	xxxxxxxx

Listing 6: Amsel Criteria and Nugent Score for BV

[Implementation notes: Continue for all subjects. List any unscheduled visit (should be for a termination visit), if exist.]

Subject ID	Treatment Group	Visit	Study Day	Amine ("whiff") test on KOH wet mount	Homogeneous Vaginal discharge characteristic of BV	Clue cells > or = 20% of the total vaginal squamous epithelial cells on saline microscopy (%)	Vaginal pH	Presence of Amsel Criteria	Clinical Diagnosis of BV	Nugent Score	BD Max BV Result
xxxxxx	TOL-463 Vaginal Insert/Placebo	00	-xx	Positive/Negative/Not Assessed	Yes/No/Not Assesses	Present/Absent/Not Assessed	xx.x/Not Assessed	0/1/2/3/4	Positive/Negative	x	Positive/Negative
		01	xx	Positive/Negative/Not Assessed	Yes/No/Not Assesses	Present/Absent/Not Assessed	xx.x/Not Assessed	0/1/2/3/4	Positive/Negative	x	Positive/Negative
		02	xx	Positive/Negative/Not Assessed	Yes/No/Not Assesses	Present/Absent/Not Assessed	xx.x/Not Assessed	0/1/2/3/4	Positive/Negative	x	Positive/Negative
		03	xx	Positive/Negative/Not Assessed	Yes/No/Not Assesses	Present/Absent/Not Assessed	xx.x/Not Assessed	0/1/2/3/4	Positive/Negative	x	Positive/Negative
		04	xx	Positive/Negative/Not Assessed	Yes/No/Not Assesses	Present/Absent/Not Assessed	xx.x/Not Assessed	0/1/2/3/4	Positive/Negative	x	Positive/Negative

Notes: Clinical diagnosis of BV is based on the presence of Amsel criteria (Positive when Amsel criteria >2). Vaginal pH > 4.5 will meet the pH criterion.

Listing 7: Individual Time to Recurrent Bacterial Vaginosis (RBV)

Subject ID	Treatment Group	Clinical Diagnosis of BV by Visit 4 [Window: Day 85-91]	Time to RBV Definition 1[a]	Time to RBV Definition 2[b]	Time to RBV Definition 3[c]
xxxxxx	TOL-463 Vaginal Insert/Placebo	Positive/Negative	x	x/N/A	x/N/A

[a] For rate of recurrence in both mITT and PP populations. For participants who experience BV recurrence by any visit, the time (in days) of BV recurrence will be defined as the midpoint between the earliest time point of a positive BV diagnosis (post-baseline) and the previous observed time-point. For participants with BV recurrence diagnosed off study, the time (in days) of BV recurrence will be defined as the midpoint between the early termination time point of a positive BV diagnosis off study (post-baseline) and the previous observed time-point. For the participants who did not experience BV recurrence by V4 will contribute the total duration they participated in the study (in days). The participants who withdrew or dropped out early will contribute the number of days they participated in the study.

[b] For secondary objective 1 in mITT population. For the participants whose RBV was diagnosed at a scheduled or unscheduled visit, their time of BV recurrence will be defined as the midpoint between the earliest time point of a positive BV diagnosis (post-baseline) and the previous observed time-point. For participants without BV recurrence at or before V4, the BV recurrence endpoint will be coded as censored, with time to recurrence defined as the elapsed time from the first dose of IP, to the earliest of: V4 time-point, the last observed time-point prior to loss to follow-up, or the time-point at which the participant became ineligible for the particular analysis population. Participants with missing time to BV recurrence will be further excluded from analyses in mITT and PP populations (time to RBV denoted as N/A in this listing), including subjects who had BV recurrence diagnosed off study or subjects who were unknown whether they used any study products.

[c] For secondary objective 1 in PP population. See b for definition of the time to RBV.

Listing 8: Individual Bacterial Vaginosis (BV) Symptoms

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Abnormal Vaginal Discharge	Vaginal Odor
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 0 - Screening (Day -15 to -8)	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 1 – Enrollment (Day 1)	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 2 – Month 2 (Days 29-35)	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 3 – Month 3 (Days 57-63)	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 4 – Month 4 (Days 85-91)	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify
xxxxx	TOL-463 Vaginal Insert /Placebo	Early Termination	xxx	No/Yes, vaginal discharge consistent with BV/Yes, other: specify	No/Yes, fishy odor consistent with BV/Yes, other: specify

Listing 9: Individual Response to Satisfaction Questionnaire

Subject ID	Treatment Group	Study Day	Completed Questionnaire	Reason Not Done	How Easy to Use	How Often to Use	How Convenient to Use	Overall Satisfaction	Would Use Again
xxxxxx	TOL-463 Vaginal Insert/Placebo	xx	Yes/No	Subject refusal/Clinic error/Subject unable to comply/Investigator decision/Other/N/A (if completed)	Extremely dissatisfied/ Very dissatisfied/ Dissatisfied/ Somewhat satisfied/ Satisfied/ Very satisfied/ Extremely satisfied	Extremely dissatisfied/ Very dissatisfied/ Dissatisfied/ Somewhat satisfied/ Satisfied/ Very satisfied/ Extremely satisfied	Extremely inconvenient/ Very inconvenient / Inconvenient / Somewhat convenient / Convenient / Very convenient / Extremely convenient	Extremely dissatisfied/ Very dissatisfied/ Dissatisfied/ Somewhat satisfied/ Satisfied/ Very satisfied/ Extremely satisfied	Yes/No

Listing 10: Demographics Data

[Implementation Note: If a subject is multi-racial, in "Race" column, note "Multiple: (list races, separated by a comma)."
For studies in infants and young children, may be more appropriate to use weeks or months for age at enrollment.]

Subject ID	Treatment Group	Age at Enrollment (years)	Ethnicity	Race
xxxxxx	TOL-463 Vaginal Insert/Placebo	XX	xxxxx	xxxxxx
xxxxxx	TOL-463 Vaginal Insert/Placebo	XX	xxxxx	xxxxxx
xxxxxx	TOL-463 Vaginal Insert/Placebo	XX	xxxxx	xxxxxx

Listing 11: Pre-Existing and Concurrent Medical Conditions

Implementation Notes:

1. Sort order will be by Actual Treatment Group, Subject ID, Concomitant Medication Number.

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxx	xxxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxx	xxxxxx

Note: This listing includes subjects who had pre-existing and/or concurrent medical conditions among all enrolled subjects.

Listing 12: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxx	Yes/No xxxxx; xx	Yes/No xxxxx; xx	xxxxxx (xxxxxx)
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxx	Yes/No xxxxx; xx	Yes/No xxxxx; xx	xxxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xxxxxx	ddMMMyyyy	ddMMMyyyy	xxxxxx	Yes/No xxxxx; xx	Yes/No xxxxx; xx	(xxxxxx)

Listing 13: Screening and Baseline Gynecologic and Sexual History - All Enrolled Subjects

Treatment Group	Subject ID	Screening			Baseline				
		Treated for BV in the Past 30 Days	Currently Use Sanitary Product	No. of times has the subject had BV in the past 12 months	First Day of Last Menstrual Period[a]	Douched or Applied Any Intravaginal Products or Medications	Had Sex Since Screening Visit	Type of Sex	How often did the subject use a condom for Vaginal Sex?
TOL-463 Vaginal Insert /Placebo	xxxxxx	Yes/No [Oral Metronidazole, Vaginal Metroge,Vaginal Clindamycin, Other:Specify]	Yes/N/A [Pads/pantyliners, Menstrual Cups, Tampons, Other: Specify]	x	DDMMMYYY/N/A	Yes/No	Yes/No	Vaginal sex, Receptive oral sex, Anal/rectal sex/ N/A	Never/Less than 50% of the time/About 50% of the time/ More than 50% of the time/Always/ N/A
TOL-463 Vaginal Insert /Placebo	xxxxxx	Yes/No [Oral Metronidazole, Vaginal Metroge,Vaginal Clindamycin, Other:Specify]	Yes/N/A [Pads/pantyliners, Menstrual Cups, Tampons, Other: Specify]	x	DDMMMYYY/N/A	Yes/No	Yes/No	Vaginal sex, Receptive oral sex, Anal/rectal sex/ N/A	Never/Less than 50% of the time/About 50% of the time/ More than 50% of the time/Always/ N/A

[a] If the subject did not have period since screening, use the response collected at the screening visit; N/A if subject is post-menopausal or amenorrheic on current hormonal birth control method.

Listing 14: Follow-up Gynecologic and Sexual History - All Enrolled Subjects

Treatment Group	Subject ID	Visit	Study Day	Douched or Applied Any Intravaginal Products or Medications Since Last Visit	Had Sex Since Last Visit	Type of Sex (Sex in the Past 24 Hours before Visit)	How often did the subject use a condom for Vaginal Sex?
TOL-463 Vaginal Insert /Placebo	xxxxxx	xx	xx	Yes/No	Yes/No	Vaginal sex (Yes/No), Receptive oral sex (Yes/No), Anal/rectal sex (Yes/No)/ N/A	Never/Less than 50% of the time/About 50% of the time/ More than 50% of the time/Always/ N/A
TOL-463 Vaginal Insert /Placebo	xxxxxx	xx	xx	Yes/No	Yes/No	Vaginal sex (Yes/No), Receptive oral sex (Yes/No), Anal/rectal sex (Yes/No),/ N/A	Never/Less than 50% of the time/About 50% of the time/ More than 50% of the time/Always/ N/A

Listing 15: Compliance Data

Implementation Notes:

Continue for all subjects.

If all subjects received the correct treatment, only display a single "Treatment Group" column.

Include data at unscheduled visits.

Study Days of Inserts Administration column: concatenate study days by a comma.

Sort by planned treatment group, USUBJID where all subjects who completed the study listed before all subject who terminated the study, Visit number.

Planned Treatment Group	Actual Treatment Group	Subject ID	Study Day of Completion /Early Termination	Visit	Number of Inserts Used/Unused	Study Days of Insert Administration	Compliant Since Last Visit[a] (Assessment Day)	Compliance Determination Throughout the Study[b]
TOL-463 Vaginal Insert/Placebo	TOL-463 Vaginal Insert/Placebo	xxxxxx	x / N/A or N/A / x	02	x/x	x, x, x, x, x, x, x, x	Yes/No (x)	Yes/No
				03	x/x	x, U, x, x, x, x, x, x	Yes/No (x)	
				04	x/x	x, x, x, x, x, x	Yes/No (x)	

Notes: For early terminated participants, compliance with study treatment will be determined through study participation.
When a study day of insert administration is unknown, it is denoted by "U".
[a] The participant did not miss >=2 consecutive or >= 3 nonconsecutive doses of IP since the last assessment, as recorded in data collection form.
[b] For cases that could not be programmatically determined, the determination of treatment compliance throughout the study was provided by a blinded case review committee.

Listing 16: Pregnancy Reports

Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xx	xxx	xxx	xxx	xxx	Y/N	Y/N	Y/N	Y/N
TOL-463 Vaginal Insert/Placebo	xxxxxx	xx	xx	xxx	xxx	xxx	xxx	Y/N	Y/N	Y/N	Y/N

Note: Maternal Complications are included in the Adverse Event Listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely Preterm Births	Very Preterm Births	Early Preterm Births	Late Preterm Births	Early Term Births	Full Term Births	Late Term Births	Post Term Births	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?
xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Y/N
xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Y/N

Note: Gravida includes the current pregnancy, para events do not.

Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?
xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Y/N	xxx
xxxxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	Y/N	xxx

Note: Congenital Anomalies are included in the Adverse Event listing.

Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?
xxxxxx	xx	xxx	xxxxxxx	Y/N	xxxxxxx	xxx	xxx	xx	Y/N	Y/N	xxxxxxx

Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion
xxxxxx	xx	xxx	xxxxx	xxxx	Y/N	xxxxxxx

Listing 17: Vital Signs

Planned Time Point	Actual Study Day	Temperature (ºC)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Weight (kg)	Height (cm)
Treatment Group: , Subject ID:						
Visit 0 - Screening (Day -15 to -8)	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx.x	xx.x
Visit 1 – Enrollment (Day 1)	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx.x	xx.x
Visit 2 – Month 2 (Days 29-35)	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	N/A	N/A
Visit 3 – Month 3 (Days 57-63)	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	N/A	N/A
Visit 4 – Month 4 (Days 85-91)	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	N/A	N/A
Early Termination	x	xx.x (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	xx (Grade 1/Grade2/Grade3)	N/A	N/A

Notes: Oral temperature and blood pressure were no longer collected at any study visits beginning with protocol version 2. Weight and Height were collected at Visit 0/Screening or Visit 1/Enrollment.
The grading scale is shown in the parentheses beneath the measurement when the measurement is in an abnormal scale.
Temperature (oral, °C) Grade 0 Normal: <38.0; Grade 1 Mild: 38.0 - 38.4; Grade 2 Moderate: 38.5 - 38.9; Grade 3 Severe: >38.9.
Hypertension (systolic) – mmHg Grade 0 Normal: 90-140; Grade 1 Mild: 141-150; Grade 2 Moderate: 151-160; Grade 3 Severe: >160.
Hypotension (systolic) – mmHg Grade 0 Normal: 90-140; Grade 1 Mild: 85-89; Grade 2 Moderate: 80-84; Grade 3 Severe: <80.
Hypertension (diastolic) – mmHg Grade 0 Normal: <91; Grade 1 Mild: 91-95; Grade 2 Moderate: 96-100; Grade 3 Severe: >100.

Listing 18: Abnormal Physical Exam Findings

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Number: Description)
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 1 – Enrollment (Day 1)	xxx	xxxxxxxx	Abdomen/Cardiovascular/heart/Extremities/ General appearance/HEENT/ Lymph node/Musculoskeletal/Neck/Neurological/Pulmonary/chest/Skin	N/A
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 2 – Month 2 (Days 29-35)	xxx	xxxxxxxx	Abdomen/Cardiovascular/heart/Extremities/ General appearance/HEENT/ Lymph node/Musculoskeletal/Neck/Neurological/Pulmonary/chest/Skin	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 3 – Month 3 (Days 57-63)	xxx	xxxxxxxx	Abdomen/Cardiovascular/heart/Extremities/ General appearance/HEENT/ Lymph node/Musculoskeletal/Neck/Neurological/Pulmonary/chest/Skin	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 4 – Month 4 (Days 85-91)	xxx	xxxxxxxx	Abdomen/Cardiovascular/heart/Extremities/ General appearance/HEENT/ Lymph node/Musculoskeletal/Neck/Neurological/Pulmonary/chest/Skin	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Early Termination	xxx	xxxxxxxx	Abdomen/Cardiovascular/heart/Extremities/ General appearance/HEENT/ Lymph node/Musculoskeletal/Neck/Neurological/Pulmonary/chest/Skin	No / Yes, AE,#: xxxxx

Note: At the enrollment visit, V1, physical exam will include weight and height measurements. At all follow-up visits, a targeted physical exam is only performed when clinically indicated

Listing 19: Listing of Clinical Diagnosis of Vulvovaginal Candidiasis (VVC) and Culture Confirmed VVC

Subject ID	Treatment Group	Planned Time Point	Actual Study Day	Edema (Severity)	Erythema (Severity)	Excoriation (Severity)	Itching (Severity)	Burning (Severity)	Irritation (Severity)	KOH Wet Mount: Yeast (Budding, Branching, Hyphae)	Clinical Diagnosis of VVC	Yeast Culture Confirmed VVC[a]	Species of Yeast Forms, If Positive Yeast Culture
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 0 – Screening (Day -15 to -8)	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 1 – Enrollment (Day 1)	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 2 – Month 2 (Days 29-35)	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 3 – Month 3 (Days 57-63)	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A
xxxxx	TOL-463 Vaginal Insert /Placebo	Visit 4 – Month 4 (Days 85-91)	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A
xxxxx	TOL-463 Vaginal Insert /Placebo	Early Termination	xxx	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	Absent/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	None/Mild/ Moderate/ Severe	Absent/Present	Yes/No	Positive/Negative /N/A	C. albicans/ C. glabrata/ Other: Specify/N/A

[a] Yeast culture was not performed if subject did not have clinical diagnosis of VVC, along with other reasons that the culture was not done, all denoted as N/A.

Listing 20: Pelvic Examination Findings

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Genital lesion consistent with active HSV or HPV	*Motile Trichomonads*	Abnormal Findings	Reported as an AE? (AE Number: Description)
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 0 - Screening (Day -15 to -8)	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 1 – Enrollment (Day 1)	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 2 – Month 2 (Days 29-35)	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 3 – Month 3 (Days 57-63)	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Visit 4 – Month 4 (Days 85-91)	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Early Termination	xxx	Present/Absent	Present/Absent	xxxxxx/None	No / Yes, AE,#: xxxxx

Listing 21: Results of STI Tests and Pap Smear at Screening/Enrollment – All Enrolled Subjects

Treatment Group	Subject ID	Normal or ASCUS HPV Negative Pap Test Within the Past 3 Years[a]	Pap Smear Performed (Study Day)	NAAT testing for chlamydia (Study Day)	NAAT testing for gonorrhea (Study Day)	NAAT testing for trichomoniasis (Study Day)
TOL-463 Vaginal Insert/Placebo	xxxxxxx	Yes/No/N/A	Normal / ASCUS HPV Negative/ Abnormal: specify (-x)	Negative/Positive/Indeterminate (-x)	Negative/Positive/Indeterminate (-x)	Negative/Positive/Indeterminate (-x)

[a] N/A if the subject is <21 years of age or has had a hysterectomy without history of cervical intraepithelial neoplasia grade 2+ (CIN2+) in the past 20 years.