Bacterial Vaginosis: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2019
Clinical/Antimicrobial

Bacterial Vaginosis: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2019
Clinical/Antimicrobial

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Bacterial Vaginosis: Developing Drugs for Treatment Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the overall development program and clinical trial designs to support development of topical and systemic drugs and biological products for the treatment of bacterial vaginosis (BV).[2]

This guidance focuses on considerations that are specific to BV drug development. This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For purposes of this guidance, references to *drugs* includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (42 U.S.C. 262) that are drugs.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. DEVELOPMENT PROGRAM

A. General Considerations

1. Drug Development Population

FDA considers postmenarchal females with clinical and laboratory-based criteria for diagnosis of BV (see sections II.B.2., Clinical Microbiology Considerations, and II.B.3., Enrollment Criteria) to be eligible for enrollment.

2. Efficacy Considerations

In general, FDA recommends two adequate and well-controlled trials to support effectiveness (see 21 CFR 314.126). If the drug is being developed for other infectious disease indication(s) in addition to BV, sponsors should discuss with FDA the potential situations in which one trial would provide evidence of effectiveness, supported by evidence of effectiveness for the other infectious disease indication(s).[4]

3. Safety Considerations

The recommended size of the safety database depends on whether the drug is administered systemically or topically, and the level of systemic absorption expected with the topical drug. If the same or greater dose and duration of therapy for treatment of BV were used in clinical trials for other infectious disease indications, typically sponsors should include the safety information from those clinical trials in the overall preapproval safety database. Sponsors should discuss the appropriate size of the preapproval safety database with FDA during clinical development, depending upon the characteristics of the topical or systemic drug.

For drugs administered topically, human safety evaluations should focus on local toxicities of the cervicovaginal area in addition to systemic toxicities.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs

The sponsor should conduct randomized, double-blind, and either placebo-controlled or active-controlled trials, with the hypothesis that the investigational drug is superior to the control treatment. Trials can be multicenter and multinational in scope; however, particular considerations may apply to such trial designs. These issues are addressed in the ICH guidance for industry *E5 Ethnic Factors in the Acceptance of Foreign Clinical Data* (June 1998) and the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND: Frequently Asked Questions* (March 2012).

[4] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

2. Clinical Microbiology Considerations

An appropriate vaginal swab specimen should be obtained for microbiologic evaluation. Specimens should be collected, processed, transported, and stored before testing according to appropriate methods.[5]

The following tests should be performed on vaginal secretion specimens collected to aid in the clinical laboratory diagnosis of BV: (1) measurement of pH; (2) the addition of a drop of 10-percent solution of potassium hydroxide (KOH) to evaluate for the presence of a characteristic *fishy amine* odor; (3) the examination for the presence of *clue cells* using a microscope at 400-times magnification of a normal saline *wet mount*; (4) measurement of pH of vaginal secretions; and (5) the examination by Gram stain for specific bacterial morphologic types (e.g., large gram-positive rods suggestive of *Lactobacillus* species, small gram-variable rods suggestive of *Bacteroides* species, curved gram-variable rods suggestive of *Mobiluncus* species, and gram-positive cocci).

3. Enrollment Criteria

The recommended enrollment criteria are outlined below:

- FDA recommends the following inclusion criteria: Postmenarchal females should have the presence of all four Amsel criteria:[6]

  (1) Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina

  (2) The presence of clue cells greater than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount[7]

  (3) Vaginal secretion pH of greater than 4.5

  (4) A fishy odor (i.e., a positive *whiff test*) of the vaginal discharge with the addition of a drop of KOH

[5] See, for example, the American Society for Microbiology, 2010, Clinical Microbiology Procedures Handbook, 3rd Edition.

[6] Amsel R, PA Totten, CA Spiegel, KC Chen, D Eschenbach, and KK Holmes, 1983, Nonspecific Vaginitis: Diagnostic Criteria and Microbial and Epidemiologic Associations, Am J Med, 74(1):14–22.

[7] Diagnostic clue cells should have *Gardnerella*-like organisms (small, nonmotile, coccobacilli) covering not only the surface of the squamous epithelial cells but also spreading out past the cell boundaries, obscuring the cytoplasmic margins and thus creating a *shaggy* appearance. The entire cell need not be covered with bacteria, but cells with organisms simply sticking to the surface without extending past the cytoplasmic margins should not be considered clue cells. Both the saline mount and the Gram stain can be easily and accurately used to determine clue cells.

To enhance the reliability for the clinical laboratory diagnosis of BV at enrollment, the Gram stain of the vaginal specimen should have a Nugent score of greater than or equal to 7.[8]

- FDA recommends the following exclusion criteria:

  – Patients with other infectious causes of vulvovaginitis (e.g., vulvovaginal candidiasis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Herpes simplex*, or human papillomavirus)

  – Patients with another vaginal or vulvar condition, which would confound the interpretation of clinical response

  – Patients who are currently receiving antibacterial therapy unrelated to BV

4. Randomization and Blinding

Eligible patients should be randomized to treatment groups at enrollment. Treatment assignment should be blinded to the patient, investigator, and microbiologist performing assessments.

5. Specific Populations

The trials should include patients of all races, as well as geriatric patients.[9] Patients with renal or hepatic impairment should be enrolled, provided pharmacokinetics of a systemic drug have been evaluated in these patients and appropriate dosing regimens have been defined, or a topically administered drug demonstrated minimal or no systemic absorption.

FDA encourages sponsors to begin discussions about pediatric clinical development plans as early as is feasible because pediatric studies are a required part of the overall drug development program and sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting or such other time as may be agreed upon by FDA and the sponsor.[10] BV is unlikely to occur in healthy premenarchal females. Inclusion of postmenarchal adolescent females in phase 3 trials may be capable of fulfilling the required pediatric clinical development plans.

---

[8] Nugent RP, MA Krohn, and SL Hillier, 1991, Reliability of Diagnosing Bacterial Vaginosis Is Improved by a Standardized Method of Gram Stain Interpretation, J Clin Microbiol, 29(2):297–301.

[9] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers* (February 2012).

[10] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the FD&C Act; 21 U.S.C. 355c), as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In general, safe and effective treatments are available for pregnant women with BV. Therefore, in general, it is appropriate to complete phase 3 clinical trials that establish safety and efficacy in nonpregnant women before trials in pregnant patients are initiated. However, if current effective treatments are unavailable, such as for a pregnant woman who is allergic to all available therapies for BV, it may be appropriate to characterize safety and pharmacokinetics of the investigational drug in pregnant women who have the potential to benefit from the investigational drug. Before sponsors consider clinical evaluations of an investigational drug in pregnant women, sponsors should complete nonclinical toxicology studies, reproductive and developmental toxicology studies, and phase 1 and phase 2 clinical trials.[11] If a woman becomes pregnant during the clinical trial, appropriate monitoring through the pregnancy and pregnancy outcome data should be collected. Infants born to women who received the investigational drug should be followed for an appropriate period of time based on available nonclinical and clinical data.

6. Dose Selection

Sponsors should conduct dose-ranging studies in BV patients in the early stages of development to help determine an adequate dosage regimen or regimens for phase 3 trials.

Specifically, sponsors should integrate findings from nonclinical studies, pharmacokinetic studies, and safety information from earlier stages of clinical development to select the dose or doses to be evaluated in phase 3 clinical trials. For systemic drugs, sponsors should evaluate information regarding pharmacokinetics in specific populations (e.g., adolescent patients, patients with renal or hepatic impairment) before initiating phase 3 trials to determine dosing in patients in those populations and to facilitate the patients' inclusion in phase 3 clinical trials.

7. Choice of Comparators

The control group for superiority trials can be a placebo or another antibacterial drug. If a vehicle control is used as the placebo for a drug administered topically, then the vehicle control should not influence the safety or efficacy evaluations (e.g., the vehicle control should not cause irritation and should not have an antibacterial effect). Appropriate active comparators can be used as a control provided superiority is demonstrated.

[11] See the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018). When final, this guidance will represent the FDA's current thinking on this topic.

8. Efficacy Endpoints

FDA characterizes the recommended primary efficacy endpoint as follows:

- Clinical cure: Resolution of the abnormal vaginal discharge, a negative whiff test, and the presence of clue cells at less than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount.[12, 13]

Sponsors also can consider the following supportive secondary endpoints:

- Nugent score of less than 4
- Responder outcome defined as clinical cure plus Nugent score of less than 4

9. Trial Procedures and Timing of Assessments

FDA recommends the following trial procedures and the timing of assessments; however, sponsors should discuss the timing of assessments for their systemic drugs with the Division of Anti-Infective Products or with the appropriate review division in CBER for CBER-regulated products:

- Entry visit: Appropriate demographic information, history and physical examination findings, a microbiological specimen, and pregnancy and safety laboratory tests should be collected at this visit; patients should be randomized and receive the study drugs at this visit.

- Visit at approximately 7 to 14 days after randomization: For systemic drugs that are administered for a short period of time (e.g., 1 to 2 days) and have a relatively short half-life (e.g., less than 24 hours), the primary efficacy endpoint should be assessed at this visit. For topical drugs that are administered for a short period of time (e.g., 1 to 2 days) and have antibacterial activity for a short time, the primary efficacy endpoint should be assessed at this visit. Adverse event information and, if appropriate, safety laboratory tests should also be collected.

- Visit at 21 to 30 days after randomization: For systemic drugs that are administered for a longer period of time (e.g., for 1 week) and/or have a long half-life (e.g., greater than 24 hours), the primary efficacy endpoint should be assessed at this visit. For topical drugs that are administered for a longer period of time (e.g., for 1 week) and/or maintain antibacterial activity for a longer time, the primary efficacy endpoint should be assessed at this visit. If this visit assesses the continued clinical response to treatment and adverse

[12] Note that there are four entry criteria, yet only three of the four criteria are used as the primary efficacy endpoint. The pH inclusion criteria are included for the purpose of enrichment of a clinical trial population most likely to have a true diagnosis of BV. Vaginal pH is not included as a component of the clinical cure for BV.

[13] For assistance with developing and using an appropriate patient-reported outome tool to assess symptoms of BV, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

events following an earlier test-of-cure clinical visit, contact with the patient by telephone may be sufficient for this visit.

FDA recommends a patient diary for the collection of information regarding drug administration, assessment of symptoms, and assessment of adverse events. Patients who have continued or worsening symptoms before the test-of-cure visit can be considered treatment failures and be offered rescue therapy for BV.

10. Statistical Considerations

In general, before initiating trials, the sponsor should submit a detailed statistical analysis plan stating the trial hypotheses and the analysis methods. The primary efficacy analysis should be based on a comparison of the proportions of patients achieving a successful efficacy outcome.

a. Analysis populations

Sponsors should consider the following definitions of analysis populations:

- Safety population — All patients who received at least one dose of the investigational drug during the trial

- Intent-to-treat population — All patients who were randomized

- Modified intent-to-treat (mITT) — All randomized patients, excluding those who subsequently demonstrate a positive test result for other concomitant vaginal or cervical infections at baseline (e.g., *C. trachomatis*, *N. gonorrhoeae*), which may interfere with the efficacy assessment for BV, or who have a baseline Nugent score less than 7.

- Per-protocol population — The population of patients who qualify for the mITT population and who follow important components of the trial (important components of the trial include adhering to the treatment and follow-up for the efficacy assessment within the prescribed time frame)

Sponsors should consider the mITT population as the primary analysis population. In general, sponsors should not consider analyses of the per-protocol populations as primary because after-randomization events or characteristics could potentially bias results in this population. However, consistency of the results should be evaluated in all patient populations. Every attempt should be made to limit the loss of patients from the trial and to follow all randomized patients for the study outcome so that the ITT analysis can be performed and there should be specific protocol-specified plans for handling missing data.

b. Sample size

The sample size is influenced by several factors including the prespecified type I and type II error, the expected success rate, and the amount by which the investigational drug is superior to the control in a superiority trial. A two-sided type I error rate of 0.05 and a type II error rate

between 0.10 and 0.20 are usually specified. Expected success rates are typically based upon results obtained in phase 2 trials or other information.

C. Other Considerations

1. Ethical Considerations

The occurrence of adverse events from antibacterial drugs can be relevant in assessing the benefit-risk to patients in a placebo-controlled trial. Rescue therapy can be incorporated into the trial design so that individual patients are treated at the time when a failure outcome is assigned; this may serve to mitigate concerns regarding inclusion of a placebo group in a trial. All trials should provide appropriate provisions for patient safety.

2. Relevant Nonclinical Considerations

Investigational drugs being studied for BV should have nonclinical data documenting activity against the implicated pathogens associated with BV. Guidances for industry provide information for sponsors on nonclinical considerations for drug development in general and also nonclinical considerations for drugs administered topically.[14]

3. Pharmacokinetic/Pharmacodynamic Considerations

Pharmacokinetic/pharmacodynamic approaches typically used to identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials for systemic bacterial infections may not be appropriate for drugs used for the treatment of BV. However, sponsors should consider the following pharmacokinetic evaluations.

For a drug administered topically in the vagina and/or the area surrounding the vagina, it is important to determine systemic drug exposure as part of the safety assessment. Evaluation of systemic exposure following topical vaginal administration can be performed in females with BV or in healthy females without BV because the extent of systemic drug absorption is not related to the presence or absence of BV.

For a drug administered systemically for treatment of BV (e.g., oral), the systemic exposure and other relevant clinical pharmacology aspects of the drug (e.g., drug-drug interactions, QT prolongation,[15] dosage adjustment in renal and/or hepatic impairment, food effect) should be adequately characterized. Sponsors should discuss with FDA the need to evaluate pertinent drug-drug interactions, particularly with oral contraceptives.

[14] See the FDA Drug guidance web page at https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs for all guidances listed in that category.

[15] See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005).