Bacterial Vaginosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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

July 2016
Clinical/Antimicrobial

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the overall clinical development program and clinical trial designs to support drugs for the treatment of bacterial vaginosis (BV).[2] This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance focuses only on developing antibacterial drugs for the treatment of symptomatic BV. There are epidemiological associations between BV and other adverse health outcomes, such as sexually transmitted infections including human immunodeficiency virus, postoperative infections, preterm birth, and other gynecological infections. Sponsors are encouraged to discuss with FDA the trial designs and drug development issues related to the development of drugs to address epidemiogically associated adverse health outcomes.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*, respectively.[4]

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

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the treatment of BV.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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.

II. DEVELOPMENT PROGRAM

A. General Considerations

1. Drug Development Population

FDA considers postmenarchal females with a clinical and microbial diagnosis of BV (see sections II.B.2 and II.B.3) to be eligible for enrollment.

2. Efficacy Considerations

In general, two adequate and well-controlled trials are recommended (see 21 CFR 314.126). If the drug is being developed for other infectious disease indications 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 indications.[5]

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. In general, for a systemically administered drug, we recommend a preapproval safety database for BV of approximately 500 patients. A topically administered drug without significant systemic absorption may need fewer patients. If the same or greater dose and duration of therapy for treatment of BV were used in clinical trials for other infectious disease indications, the safety information from those clinical trials typically should be included in the overall preapproval safety database. Sponsors should discuss the appropriate size of the preapproval safety database with FDA during clinical development.

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

[5] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs

Trials should be randomized, double-blinded, and either placebo-controlled or active-controlled, 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* and the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions*.

2. Clinical Microbiology Considerations

An appropriate vaginal swab clinical specimen should be obtained for microbiologic evaluation. Specimens should be collected, processed, and transported according to appropriate methods.[6]

The following tests should be performed on specimens collected to aid in the diagnosis of BV: (1) the addition of a drop of 10-percent solution of potassium hydroxide (KOH) to evaluate for the presence of a characteristic *fishy amine* odor; (2) the examination for the presence of *clue cells* using a microscope at 400-times magnification of a normal saline *wet mount*; and (3) 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 as follows:

- Inclusion criteria: postmenarchal females should have the presence of all four Amsel criteria:[7]

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

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

[7] 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.

(2) The presence of clue cells greater than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount[8]

(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

To enhance the reliability for the diagnosis of BV at enrollment, the Gram stain of the vaginal specimen should have a Nugent score of greater than or equal to 7.[9]

- The following exclusion criteria are recommended:

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

  – 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.[10] Patients with renal or hepatic impairment can be enrolled, provided pharmacokinetics of a drug with systemic absorption have been evaluated in these patients and appropriate dosing regimens have been defined, or pharmacokinetics of a drug administered topically demonstrated minimal or no systemic absorption.

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[8] 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.

[9] 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 Micro, 29(2):297-301.

[10] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

Sponsors are encouraged to begin discussions about their pediatric clinical development plan 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.[11] BV is unlikely to occur in healthy premenarchal girls. Postmenarchal adolescent girls with BV should be included in phase 3 trials, if appropriate. Inclusion of adolescents in phase 3 trials may be capable of fulfilling the required pediatric clinical development plans.

In general, safe and effective treatments are available for pregnant patients with BV. Therefore, it is generally appropriate to complete phase 3 clinical trials that establish safety and efficacy in nonpregnant patients before trials in pregnant patients are initiated. However, if current effective treatments are unavailable, such as a pregnant patient who has allergy to all available therapies for BV, it may be appropriate to characterize safety and pharmacokinetics of the investigational drug in pregnant patients who have the potential to benefit from the investigational drug. Before sponsors consider clinical evaluations of an investigational drug in pregnant women, nonclinical toxicology studies, reproductive and developmental toxicology studies, and phase 1 and phase 2 clinical trials should be completed. 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 integrate findings from nonclinical studies, pharmacokinetics, and safety information from earlier stages of clinical development to select the dose or doses to be evaluated in phase 3 clinical trials. Information regarding pharmacokinetics in specific populations (e.g., adolescent patients, patients with renal or hepatic impairment) should be evaluated before initiation of phase 3 to determine whether dose adjustments are necessary and may prevent the exclusion of these patients from the 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 Pediatric Research Equity Act (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c), as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (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 Pediatric Study Plans*. When final, this guidance will represent FDA's current thinking on this topic.

8. Efficacy Endpoints

The recommended primary efficacy endpoint is characterized as follows:

> Clinical cure: resolution of the abnormal vaginal discharge, 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]

Sponsors also can consider the following supportive secondary endpoints for BV:

- 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

The following points outline the recommended trial procedures and the timing of assessments:

- 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 clinical trial treatment at this visit.

- Visit at approximately 7 to 14 days after randomization: This visit should assess the primary efficacy endpoint and should be the test-of-cure visit. Adverse event information and, if appropriate, safety laboratory tests should also be collected.

- Visit at 21 to 30 days after randomization: This visit should assess the continued clinical response to treatment and adverse events. Contact with the patient by telephone may be sufficient for this visit.

A patient diary is recommended for the collection of information regarding investigational drug administration, assessment of symptoms, and adverse events. Patients who have continued or worsening symptoms before the test-of-cure visit can be assigned as a treatment failure and offered rescue therapy for BV.

10. Statistical Considerations

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

[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 is 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.

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 patients who adhere to the treatment and follow up for the efficacy assessment within the prescribed time frame)

The mITT population should be considered 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. If any missing patient outcome data is anticipated, there should be plans for handling that in the protocol.

b. Sample size

The sample size is influenced by several factors including the prespecified type I and type II error, the heterogeneity of the 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 risk-benefit 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 (e.g., *Gardnerella vaginalis*, *Mycoplasma hominis*). Guidances for industry provide information for sponsors on nonclinical considerations for drug development in general and also nonclinical considerations for drugs administered topically.[13]

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, the following pharmacokinetic evaluations should be considered for such drugs used for the treatment of BV.

For a drug administered topically into 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 it is deemed that 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,[14] 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. In addition, dose-ranging studies in BV patients can be considered as an option in the early stages of development to help determine an adequate dosage regimen to bring forth in later trials.

[13] See the Pharmacology/Toxicology guidance Web Page at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm. For example, see the guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products*. Given the unique characteristics of a topical administration, sponsors also may wish to refer to the guidance for industry *Nonclinical Pharmacology/Toxicology Development of Topical Drugs Intended to Prevent the Transmission of Sexually Transmitted Diseases (STD) and/or for the Development of Drugs Intended to Act as Vaginal Contraceptives*.

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