Vulvovaginal Candidiasis: 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)

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Clinical/Antimicrobial

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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
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Contains Nonbinding Recommendations

Vulvovaginal Candidiasis: 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 clinical development program and clinical trial designs to support drugs for treating vulvovaginal candidiasis (VVC).[2]

In general, this guidance focuses only on treating VVC. This guidance does not discuss clinical development programs focused on preventing or reducing the recurrence of VVC. Sponsors should discuss the clinical development of such programs with FDA.

This guidance focuses on considerations that are specific to VVC drug development. This guidance does not discuss trial designs for development programs for nonprescription treatments of VVC, nor does it discuss 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 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] 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

This section discusses clinical development considerations, including the target population, efficacy, and safety in developing drugs for treating VVC.

1. Drug Development Population

Sponsors should enroll postmenarchal females with a clinical diagnosis of VVC. Sponsors should also discuss with FDA whether they plan to include in the trial population patients who have HIV/AIDS or diabetes mellitus.

2. Efficacy Considerations

In general, FDA recommends two adequate and well-controlled trials to demonstrate efficacy (see 21 CFR 314.126). If the drug is being developed for other indications, 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 indications.[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 product. If the same or greater dose and duration of therapy for treating VVC were used in clinical trials for other infectious disease indications, sponsors should include the safety information from those clinical trials in the overall preapproval safety database. Sponsors should also discuss the appropriate size of the preapproval safety database with FDA during clinical development, depending on the characteristics of the topical or systemic product.

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

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs

Trials should be randomized, double-blinded, and either placebo-controlled or active-controlled, using a superiority design. If a noninferiority trial is being considered, sponsors should discuss such a trial design with the Agency.[5]

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

[5] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

2. Clinical Microbiology Considerations

Sponsor should obtain an appropriate vaginal swab specimen for microbiologic evaluation. Sponsors should also collect, process, transport, and store specimens as needed before testing according to appropriate methods.[6]

Specimens collected to aid diagnosing VVC in the clinical laboratory should be examined microscopically for the presence of yeast (e.g., a wet mount prepared in a potassium hydroxide solution (KOH)) and should be cultured using standard fungal media.[7] Yeast grown in culture should be identified to species level and tested for susceptibility to appropriate antifungal drugs, using standard laboratory methods such as those recommended by the Clinical and Laboratory Standards Institute (CLSI).[8]

3. Enrollment Criteria

Inclusion criteria should include postmenarchal females who have a clinical diagnosis of VVC defined as:

- Two or more of the following signs and symptoms of VVC: itching, burning, irritation, edema, redness, or excoriation[9]
- KOH or saline preparation from the inflamed vaginal mucosa or secretions demonstrating yeast forms (hyphae or pseudohyphae) or budding yeasts
- Vaginal pH less than or equal to 4.5

The following patients should be excluded:

- Patients with other infectious causes of vulvovaginitis (e.g., bacterial vaginosis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, Herpes simplex*, or human papillomavirus) or with mixed infections
- Patients who were treated for VVC within the past 14 days

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

[7] Clinical and Laboratory Standards Institute (CLSI), 2008, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard — Third Edition, CLSI document M27-A3, Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA.

[8] CLSI, 2012, Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Fourth Informational Supplement, CLSI document M27-S4, Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

[9] In general, we recommend that at least two signs or symptoms be of at least moderate severity.

- Patients who are currently receiving antifungal therapy unrelated to VVC

4. Randomization and Blinding

Eligible patients should be randomized to treatment groups at enrollment. All trials should be multicenter and double-blinded to control for potential biases.

5. Specific Populations

Sponsors should include patients of all races, as well as geriatric patients, in the trials.[10] Additionally, sponsors can enroll patients with renal or hepatic impairment if appropriate dosing regimens have been defined for systemic products.

Sponsors are encouraged to begin discussing 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] VVC is unlikely to occur in healthy premenarchal girls. Sponsors should include in phase 3 clinical trials postmenarchal adolescent girls with VVC, if appropriate. Including adolescents in phase 3 clinical trials may fulfill the required pediatric clinical development plans.

In general, safe and effective treatments are available for pregnant women with VVC. Therefore, it is generally acceptable for sponsors to complete phase 3 clinical trials that establish safety and efficacy in nonpregnant women before initiating trials in pregnant women. However, if current effective therapy is unavailable, such as for a pregnant woman who is allergic to all available drugs for treating VVC, it may be appropriate for sponsors to offer the pregnant woman the investigational drug. Before considering using 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. Additionally, sponsors should follow infants born to mothers who received the investigational drug for an appropriate period of time based on available nonclinical and clinical data.

6. Dose Selection

Sponsors should integrate findings from nonclinical studies, pharmacokinetic and dose-ranging studies, and safety information from earlier stages of clinical development to select the dose or doses to be evaluated in phase 3 clinical trials. Sponsors should also evaluate the pharmacokinetics of the drug in specific populations (e.g., adolescent patients, patients with renal

[10] 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).

[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* (March 2016). When final, this guidance will represent FDA's current thinking on this topic.

or hepatic impairment) before initiating phase 3 clinical trials to determine dosing in patients in those populations and to facilitate the patients' inclusion in phase 3 clinical trials.

7. Choice of Comparators

For most superiority trials, the control group should be an oral placebo for an oral drug or a vehicle control for a drug administered topically. 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 antifungal effect). Appropriate active comparators can be used as a control provided superiority is demonstrated.

8. Efficacy Endpoints

The primary efficacy endpoint should be clinical cure, defined as the absence of all signs and symptoms of VVC.[12]

Sponsors should consider the following secondary endpoints:

- Vaginal swab culture negative for growth of *Candida* species
- Responder outcome, defined as absence of signs and symptoms plus vaginal swab culture negative for growth of *Candida* species

9. Trial Procedures and Timing of Assessments

The following are the recommended trial procedures and the timing of assessments:

- Entry visit: Sponsors should collect appropriate demographic information, history and physical examination findings, a microbiological specimen, and safety laboratory tests (including pregnancy testing). Sponsors should also randomize patients and give them the investigational or control treatment.
- On-therapy assessment: Sponsors should use telephone calls or diary card entries to assess symptom improvement/resolution and adverse effects.
- Patient 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), sponsors should assess the primary efficacy endpoint at this visit (can serve as the test-of-cure visit). For topical drugs that are administered for a short period of time (e.g., 1 to 2 days) and have antifungal activity for a short time, sponsors should assess the primary efficacy endpoint at this visit. Sponsors should also collect adverse-event information and, if appropriate, safety laboratory tests.

[12] Please refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009) if sponsors would like to propose a more clinically relevant endpoint regarding symptom improvement/resolution.

- Patient visit at 21 to 30 days after randomization: For systemic drugs that are administered for a longer period of time (e.g., 1 week) and/or have a long half-life (e.g., greater than 24 hours), sponsors should assess the primary efficacy endpoint at this visit (can serve as the test-of-cure visit). For topical drugs that are administered for a longer period of time (e.g., 1 week) and/or maintain antifungal activity for a longer time, sponsors should assess the primary efficacy endpoint at this visit. If the test-of-cure visit occurs at the earlier time point (e.g., 7 to 14 days after randomization), then sponsors can assess at this (21 to 30 days) visit the continued clinical response to treatment and adverse-event occurrence. In such a scenario, the 21- to 30-day visit can be conducted by telephone.

FDA recommends a patient diary for collecting information about investigational drug administration, assessment of symptoms, and adverse events. Sponsors can assign patients who have continued or worsening symptoms before the test-of-cure visit as a treatment failure and can offer them rescue therapy for VVC.

10. Statistical Considerations

In general, sponsors should submit a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before initiating trial. 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 who have *Candida* species isolated on culture of vaginal specimen at baseline

- Per-protocol population: Patients who qualify for the mITT population and who follow important components of the trial, which include patients who adhere to the treatment and follow up for the efficacy assessment within the prescribed time frame

Sponsors should consider the mITT population the primary analysis population. In general, sponsors should not consider analyses of the per-protocol populations as primary because postrandomization events or characteristics could potentially bias results in this population. However, sponsors should evaluate the consistency of the results in all patient populations. Sponsors should also make every attempt to limit the drop out of patients from the trial and should specify in the protocol the method 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 expected to be superior to the control. 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 on results obtained in phase 2 clinical trials or other information.

C. Other Considerations

1. Ethical Considerations

Rescue therapy can be incorporated into the placebo-controlled trial design so that individual patients are treated at the time a failure outcome is assigned, which may mitigate ethical concerns about including a placebo group in a trial. All trials should provide appropriate provisions for patient safety.

2. Relevant Nonclinical Considerations

Investigational drugs being studied for VVC should have nonclinical data documenting activity against *Candida* species.[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 infections may not be appropriate for drugs used for treating VVC. However, sponsors should consider the following pharmacokinetic evaluations.

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

For a drug administered systemically for treating VVC (e.g., oral), sponsors should adequately characterize the systemic/vaginal 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). Sponsors should discuss with FDA the need to evaluate pertinent drug-drug interactions, particularly with oral contraceptives. Additionally, sponsors

[13] See the Pharmacology/Toxicology guidance web page at https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs.

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

should conduct in the early stages of development (e.g., phase 2) dose-ranging studies with exposure-response analyses for both efficacy and safety in VVC patients to inform dosage in later trials.