
Vulvovaginal Candidiasis: 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DRAFT GUIDANCE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**

Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry

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Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry¹

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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program and clinical trial designs to support drugs for the treatment of vulvovaginal candidiasis (VVC).² This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and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

In general, this guidance focuses only on developing antifungal drugs for the treatment of uncomplicated VVC, generally defined as a single episode of vaginal inflammation caused by *Candida* yeast in an otherwise healthy female. For complicated VVC (e.g., patients who have recurrent VVC, defined as having four or more episodes of VVC in a 1-year time frame), the dose, duration, or formulation of antifungal treatment may be different in comparison to uncomplicated VVC. Sponsors should discuss with FDA the clinical development programs for treatment of complicated VVC.

This guidance does not discuss trial designs for development programs for nonprescription treatments of VVC. This guidance also does not contain discussion of general issues in drug development or general issues of statistical analysis or clinical trial design. Those topics are

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 VVC.

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35 addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10*
36 *Choice of Control Group and Related Issues in Clinical Trials*, respectively.⁴
37

38 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
39 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
40 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
41 the word *should* in Agency guidances means that something is suggested or recommended, but
42 not required.
43

44
45 **II. DEVELOPMENT PROGRAM**

46
47 **A. General Considerations**

48
49 *1. Drug Development Population*
50

51 Sponsors should enroll postmenarchal females with a clinical diagnosis of uncomplicated VVC.
52 Sponsors should discuss with FDA if the trial population plans to include patients who have
53 HIV/AIDS or diabetes mellitus.
54

55 *2. Efficacy Considerations*
56

57 In general, two adequate and well-controlled trials are recommended for the demonstration of
58 efficacy (see 21 CFR 314.126). If the drug is being developed for other infectious disease
59 indications, sponsors should discuss with FDA the potential situations in which one trial would
60 provide evidence of effectiveness, supported by evidence of effectiveness for the other infectious
61 disease indications.⁵
62

63 *3. Safety Considerations*
64

65 The recommended size of the safety database depends on whether the drug is administered
66 systemically or topically, and the level of systemic absorption. If the same therapy for treatment
67 of VVC were used in clinical trials for other infectious disease indications, the safety information
68 from those clinical trials typically can be included in the overall preapproval safety database.
69 Sponsors should discuss the appropriate size of the preapproval safety database with FDA during
70 clinical development.
71

72 For drugs administered topically, human safety evaluations should focus on local toxicities of the
73 cervicovaginal area in addition to systemic toxicities.
74

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>.

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

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75 **B. Specific Efficacy Trial Considerations**

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77 1. *Clinical Trial Designs*

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79 Trials should be randomized, double-blinded, and either placebo-controlled or active-controlled,
80 using a superiority design.

81

82 2. *Clinical Microbiology Considerations*

83

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

86

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

92

93 3. *Enrollment Criteria*

94

95 Inclusion criteria for VVC trials should include postmenarchal females who have a clinical
96 diagnosis of VVC, defined as having a white or creamy vaginal discharge plus the following
97 findings:

98

- 99 • Two or more of the following signs and symptoms of VVC that are characterized as
100 *moderate* or *severe*: itching, burning, irritation, edema, redness, or excoriation⁹
- 101
- 102 • KOH or saline preparation from the inflamed vaginal mucosa or secretions revealing
103 yeast forms (hyphae or pseudohyphae) or budding yeasts
- 104
- 105 • Normal vaginal pH (greater than or equal to 4.5)

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 There should be at least two signs or symptoms are of at least moderate severity. Signs and symptoms can be rated on a scale and evaluated using a score based on a numerical rating of severity (absent=0; mild=1; moderate=2; severe=3) for each symptom. The purpose of the qualitative evaluation of signs and symptoms at baseline is to establish a patient population with sufficient severity of uncomplicated VVC for trial enrollment. See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

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The following patients should be excluded from VVC trials:

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

The trials should include patients of all races, as well as geriatric patients.¹⁰ Patients with renal or hepatic impairment can be enrolled if appropriate dosing regimens have been defined.

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

Uncomplicated VVC is unlikely to occur in healthy premenarchal girls. Postmenarchal adolescent girls with VVC should be included in phase 3 trials, if appropriate. Inclusion of adolescents in phase 3 trials is capable of fulfilling the required pediatric clinical development plans.

In general, safe and effective treatments are available for pregnant patients with VVC. Therefore, it is generally acceptable 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 therapy is unavailable, such as a pregnant patient who is allergic to all available drugs for treatment of VVC, it may be appropriate to offer the investigational drug in the pregnant patient. Before sponsors consider use 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 mothers who received the

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*.

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.

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144 investigational drug should be followed for an appropriate period of time based on available
145 nonclinical and clinical data.

146
147 6. *Dose Selection*

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149 Sponsors should integrate findings from nonclinical studies, pharmacokinetics, and safety
150 information from earlier stages of clinical development to select the dose or doses to be
151 evaluated in phase 3 clinical trials. The pharmacokinetics of the drug in specific populations
152 (e.g., adolescent patients, patients with renal or hepatic impairment) should be understood before
153 initiation of phase 3 trials to determine whether dose adjustments are necessary. This evaluation
154 may prevent the exclusion of such patients from the phase 3 clinical trials.

155
156 7. *Choice of Comparators*

157
158 For most superiority trials, the control group for VVC should be an oral placebo or a vehicle
159 control for a drug administered topically. The vehicle control should not influence the safety or
160 efficacy evaluations (e.g., the vehicle control should not cause irritation and should not have an
161 antifungal effect). Appropriate active comparators can be used as a control provided superiority
162 is demonstrated.

163
164 8. *Efficacy Endpoints*

165
166 The primary efficacy endpoint should be clinical cure, defined as the absence of all signs and
167 symptoms of VVC.

168
169 Sponsors should consider the following secondary endpoints:

- 170
171 • Vaginal swab culture negative for growth of *Candida* species
172
173 • Responder outcome, defined as absence of signs and symptoms plus vaginal swab
174 culture negative for growth of *Candida* species
175

176 9. *Trial Procedures and Timing of Assessments*

177
178 The following bullet points outline the recommended trial procedures and the timing of
179 assessments:

- 180
181 • Entry visit: Appropriate demographic information, history and physical examination
182 findings, a microbiological specimen, and safety laboratory tests (including pregnancy
183 testing) should be collected at this visit; patients should be randomized and receive the
184 investigational drug or control treatment at this visit.
185
186 • On-therapy assessment: Telephone calls or diary card entries should be used to assess for
187 adverse effects.
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- Test-of-cure visit, approximately 7 to 14 days after randomization: This visit should assess the primary efficacy endpoint. Adverse effect information and, if appropriate, safety laboratory tests should also be collected. The timing of this visit depends on the total duration of antifungal therapy.
 - 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.

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

202

203 10. *Statistical Considerations*

204

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

208

209 a. Analysis populations

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211 Sponsors should consider the following definitions of analysis populations:

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- 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 — 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)

226 The mITT population should be considered the primary analysis population. In general,
227 sponsors should not consider analyses of the per-protocol populations as primary because
228 postrandomization events or characteristics could potentially bias results in this population.
229 However, consistency of the results should be evaluated in all patient populations. Every attempt
230 should be made to limit the loss of patients from the trial. The method for handling missing data
231 should be specified in the protocol.

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233 b. Sample size

234
235 The sample size is influenced by several factors including the prespecified type I and type II
236 error, the expected success rate, and the amount by which the investigational drug is expected to
237 be superior to the control. A two-sided type I error rate of 0.05 and a type II error rate between
238 0.10 and 0.20 are usually specified. Expected success rates are typically based upon results
239 obtained in phase 2 trials or other information.

240
241 **C. Other Considerations**

242
243 1. *Ethical Considerations*

244
245 Rescue therapy can be incorporated into the placebo-controlled trial design so that individual
246 patients are treated at the time a failure outcome is assigned: this may serve to mitigate ethical
247 concerns regarding inclusion of a placebo group in a trial. All trials should provide appropriate
248 provisions for patient safety.

249
250 2. *Relevant Nonclinical Considerations*

251
252 Investigational drugs being studied for VVC should have nonclinical data documenting activity
253 against *Candida* species. Guidance for industry provides information for sponsors on nonclinical
254 considerations for drug development in general and also nonclinical considerations for drugs
255 administered topically.¹²

256
257 3. *Pharmacokinetic/Pharmacodynamic Considerations*

258
259 Pharmacokinetic/pharmacodynamic approaches typically used to identify appropriate dosing
260 regimens for evaluation in phase 2 and phase 3 clinical trials for systemic infections may not be
261 appropriate for drugs used for the treatment of VVC. However, the following pharmacokinetic
262 evaluations should be considered.

263
264 For a drug administered topically into the vagina and/or the area surrounding the vagina, it is
265 important to determine systemic drug exposure as part of the safety assessment. Evaluation of
266 systemic exposure following topical vaginal administration can be performed in females with
267 VVC or in healthy females without VVC because it is deemed that the extent of systemic drug
268 absorption is not related to the presence or absence of VVC.

269

¹² 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*; and, given the unique characteristics of a topical administration, sponsors of a topical drug may want to refer to the discussions of nonclinical safety evaluations in 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*. See also the guidance for industry *Vaginal Microbicides: Development for the Prevention of HIV Infection* on the Clinical/Antimicrobial guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm>.

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270 For a drug administered systemically for treatment of VVC (e.g., oral), the systemic/vaginal
271 exposure and other relevant clinical pharmacology aspects of the drug (e.g., drug-drug
272 interactions, QT prolongation,¹³ dosage adjustment in renal and/or hepatic impairment, food
273 effect) should be adequately characterized. Sponsors should discuss with FDA the need to
274 evaluate pertinent drug-drug interactions, particularly with oral contraceptives. In addition,
275 dose-ranging studies in VVC patients can be considered as an option in the early stages of
276 development to help determine an adequate dosage regimen to bring forth in later trials.
277

¹³ See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.