Uncomplicated Gonorrhea: 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)

August 2015
Clinical/Antimicrobial

Uncomplicated Gonorrhea: 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
Tel: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

August 2015
Clinical/Antimicrobial

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Uncomplicated Gonorrhea: 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 create 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 clinical development of drugs for the treatment of uncomplicated gonorrhea.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for antibacterial drugs for the treatment of uncomplicated gonorrhea.

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* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, 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 Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Sexually transmitted infectious diseases are common in the United States. The Centers for Disease Control and Prevention (CDC) estimated that approximately 820,000 incident cases of gonorrhea occurred in 2008 in the United States (Satterwhite, Torrone, et al. 2013). Antibacterial drug susceptibility profiles for *Neisseria gonorrhoeae* have continued to change to more resistant isolates since the 1940s (Kirkcaldy, Bolan, et al. 2013; Del Rio, Hall, et al. 2012). The potential for gonorrhea to become resistant to all currently available antibacterial drugs (Bolan, Sparling, et al. 2012) highlights the need for the development of new antibacterial drugs for the treatment of gonorrhea.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Development Considerations

Sponsors involved in clinical development of an investigational antibacterial drug with in vitro activity against *N. gonorrhoeae* are encouraged to consider drug development for the treatment of uncomplicated gonorrhea.

2. Drug Development Population

The clinical development population should include patients with uncomplicated urethral, cervical, rectal, or pharyngeal infections caused by *N. gonorrhoeae*.

3. Efficacy Considerations

A single adequate and well-controlled noninferiority trial can provide evidence of effectiveness.[4] Sponsors should discuss with FDA the independent confirmatory evidence that would provide support for the evidence of effectiveness (e.g., the results of a trial in another infectious disease indication). If treatment of uncomplicated gonorrhea is the only indication being sought for an investigational drug, in general we recommend two adequate and well-controlled trials; however, in certain circumstances, a compelling outcome in a single trial might provide evidence of effectiveness (e.g., showing superiority to a control drug in a planned noninferiority trial).

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

4. Safety Considerations

In general, we recommend a preapproval safety database of approximately 500 patients at the proposed single dose, and a targeted duration of safety evaluation is approximately 3 to 7 days following the single dose administration.[5] If the same or greater dose and duration of therapy for treatment of uncomplicated gonorrhea were used in clinical trials for other infectious disease indications, the safety information from clinical trials in other infectious disease indications can contribute to the overall preapproval safety database.[6] Sponsors should discuss with FDA the appropriate size of the preapproval safety database during clinical development. Sponsors should consider the option of unequal randomization in the efficacy trial (e.g., 2:1, 3:2) as a means of augmenting the overall safety database.

B. Specific Efficacy Trial Considerations

1. Trial Design, Populations, and Entry Criteria

Trials should be prospective, randomized, and double-blinded. The trial population should include patients with evidence of uncomplicated gonorrhea (i.e., infection of the urethra, cervix, pharynx, or rectum caused by *N. gonorrhoeae*). The entry criteria can be broad (e.g., including any patient who has uncomplicated gonorrhea) or focused (e.g., patients who have urethritis or cervicitis).

Some patients who have gonococcal infections are asymptomatic, and infection may be established by tests during routine health care visits. Such patients can be included in clinical trial populations.

2. General Exclusion Criteria

The following patients should be excluded:

- Patients who have gonococcal infections that require a different dose or duration of treatment (e.g., disseminated gonococcal infection, pelvic inflammatory disease, epididymitis, conjunctivitis)

- Patients who have received any effective antibacterial therapy for the treatment of gonorrhea

[5] See the draft guidance for industry *Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations*. When final, this guidance will represent FDA's current thinking on this topic.

[6] See the guidance for industry *Premarketing Risk Assessment*.

3. Clinical Microbiology Considerations

An adequate clinical specimen should be obtained for microbiologic evaluation, including Gram stain, culture, and in vitro antibacterial susceptibility testing. Specimens should be collected, processed, and transported according to recognized methods (American Society for Microbiology 2011). Direct inoculation of the specimen on both selective and nonselective media maximizes the sensitivity, particularly for cervical specimens. Methods to reliably exclude infection or colonization by *Neisseria meningitidis* are recommended for specimens from the rectum or pharynx. This microbiological information is important for characterizing *N. gonorrhoeae* isolates and for developing susceptibility test interpretive criteria.

For clinical trials evaluating an investigational drug, nucleic acid amplification tests (NAATs) should not replace culture for the diagnosis of gonococcal infection and establishment of a test of cure in which important microbiological information is obtained and evaluated by culture (e.g., in vitro susceptibility testing). However, NAATs or other rapid diagnostic tests can be used to select patients for enrollment. Subsequent confirmation of *N. gonorrhoeae* by culture can be used to define the primary analysis populations.

The clinical trial of an antibacterial drug may also provide an opportunity to contribute to development and evaluation of a new diagnostic test. Sponsors interested in using a clinical trial in patients with uncomplicated gonorrhea as a means for evaluation of a new diagnostic test are encouraged to discuss this with FDA.

4. Randomization, Stratification, and Blinding

Eligible patients should be randomized to treatment groups at enrollment. Sponsors should consider the option of stratification before randomization to ensure that treatment groups are balanced with regard to infection site and sex (e.g., women with cervicitis, men with urethritis). All trials should be multicenter and double-blinded to control for potential biases unless blinding is not feasible.

5. Specific Populations

The trials should include patients of both sexes and all races. Patients who have the human immunodeficiency virus infection can be included in clinical trials.

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.[7]

[7] 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 the FDA's current thinking on this topic.

Adolescents should be included during preapproval drug development. Adolescents can be enrolled in phase 3 clinical trials, if appropriate.

In general, safe and effective treatments are available for pregnant patients with uncomplicated gonorrhea. 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 treatment options are not available for pregnant patients with uncomplicated gonorrhea (e.g., pregnant patients infected with *N. gonorrhoeae* resistant to all available antibacterial drugs), it may be appropriate to characterize safety and pharmacokinetics in pregnant patients with uncomplicated gonorrhea who have the potential to benefit from the investigational drug. Before sponsors consider clinical evaluations of an investigational drug in pregnant women, they should complete nonclinical toxicology studies, reproductive and developmental toxicology studies, and phase 1 and phase 2 clinical trials. Infants born to mothers who received the investigational drug should be followed by the trial's investigators until at least 12 months of age.

6. Dose Selection

Drugs for the treatment of uncomplicated gonorrhea generally should be administered as a single dose. 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. The pharmacokinetics of the drug 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. This evaluation may prevent the exclusion of such patients from the phase 3 clinical trials.

7. Use of Active Comparators and Concomitant Therapy

The active comparator in a phase 3 controlled trial should be an antibacterial drug that is recommended for treatment of uncomplicated gonorrhea by authoritative scientific bodies based on clinical evidence and that reflects current clinical practice.[8]

In general, treatment for *Chlamydia trachomatis* should be offered to all patients with a diagnosis of uncomplicated gonorrhea (Del Rio, Hall, et al. 2012). Sponsors should discuss with FDA the choice and timing of concomitant therapy if the investigational drug does not have activity against *C. trachomatis*.

8. Efficacy Endpoint

The primary efficacy endpoint should be the establishment of a negative culture at the infection site or sites approximately 3 to 7 days after receipt of antibacterial drug therapy (microbiological cure).

[8] The CDC publishes guidelines for the treatment of sexually transmitted diseases and periodically updates those guidelines (see, for example, Del Rio, Hall, et al. 2012).

9. Secondary Endpoints

Suggested secondary endpoints for the trial include the following:

- The results of a NAAT following treatment
- Symptom resolution in the subgroup of patients who have baseline symptoms attributable to uncomplicated gonorrhea[9]

10. Trial Procedures and Timing of Assessments

The following bullet 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 safety laboratory tests should be collected at this visit; patients should receive investigational antibacterial drug treatment at this visit.
- Visit at approximately 3 to 7 days after receipt of treatment: This visit should assess microbiological cure using a microbiological specimen from the baseline infected site or sites. Adverse effect information and, if appropriate, safety laboratory tests should also be collected.

11. 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 microbiological cure.

a. Analysis populations

Sponsors should consider the following definitions of analysis populations for uncomplicated gonorrhea trials:

- Safety population — All patients who received the investigational drug during the trial
- Intent-to-treat population — All patients who were randomized
- Microbiological intent-to-treat (micro-ITT) population — All patients randomized who have *N. gonorrhoeae* isolated on baseline culture
- Per-protocol population — Patients who follow important components of the trial

[9] Symptoms and their resolutions, although important to evaluate as a secondary endpoint, are not well defined and reliable in uncomplicated gonorrhea for the following reasons: (1) some patients who have uncomplicated gonorrhea are asymptomatic; and (2) patients who failed antibacterial drug treatment in the setting of drug resistance had symptom resolution (see, for example, Allen, Mitterni, et al. 2013).

- Per-protocol microbiologically evaluable population — Patients who follow important components of the trial and have *N. gonorrhoeae* isolated on baseline culture (e.g., micro-ITT patients who follow important components of the trial)

The micro-ITT 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 potentially could 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 such that the micro-ITT population and per-protocol microbiologically evaluable population are similar. The method for handling missing data should be specified in the protocol.

b. Noninferiority margins

Noninferiority trials are informative only if there is reliable and reproducible evidence of treatment effect for the active-controlled drug.[10] A noninferiority margin for the primary efficacy endpoint of microbiological cure based on the demonstration of a negative culture result is supported by historical data (see the Appendix). Sponsors should discuss the selection of the noninferiority margin with FDA in advance of trial initiation.

c. Sample size

An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately 190 patients per group based on a noninferiority margin selection of 10 percent and a microbiological cure rate in the micro-ITT population of 90 percent in the control group (see the results from the clinical trials in Table 1 of the Appendix). The trial should rule out a greater than 10 percent inferiority of the investigational drug to the control drug (upper bound of the two-sided 95 percent confidence interval (CI) for the microbiological cure rate of the control drug minus the investigational drug).

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

The pharmacokinetic (PK)/pharmacodynamic (PD) characteristics of the drug should be evaluated in nonclinical models (e.g., in vitro PK/PD models, animal models of infection). Nonclinical PK/PD assessments should be integrated with findings from phase 1 PK assessments to help identify appropriate dose and dosing regimens for evaluation in phase 2 and phase 3 clinical trials. Collection of PK data in phase 2 trials can be used to explore dose-response relationships to support dose selection for further evaluation in phase 3 trials.

[10] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent FDA's current thinking on this topic.

2. Investigational Drugs With Activity Against N. gonorrhoeae and C. trachomatis

Investigational drugs that have potential to treat both gonorrhea and chlamydia can have concurrent clinical development programs. For example, a phase 3 trial can enroll patients with clinical evidence of infection caused by *N. gonorrhoeae* and/or *C. trachomatis*. NAATs or other rapid diagnostic testing could direct patients into groups intended to evaluate treatment of gonorrhea, chlamydia, or both. Sponsors should discuss a concurrent phase 3 development program with FDA.

3. Labeling Considerations

The labeled indication for the treatment of uncomplicated gonorrhea generally should reflect the population for which there is substantial evidence of safety and effectiveness, which is usually based on the types of patients evaluated in the clinical development program.

For example, if the clinical development program evaluated patients who had cervicitis or urethritis (and patients with oropharyngeal or rectal gonorrhea were specifically excluded from drug development), the indication should reflect that patient population:

> *"Drug X is indicated for the treatment of uncomplicated gonorrhea (cervicitis/urethritis) caused by susceptible strains of Neisseria gonorrhoeae."*

REFERENCES

Allen VG, L Mitterni, C Seah, et al., 2013, Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada, JAMA, 309(2):163-170.

American Society for Microbiology, 2011, Manual of Clinical Microbiology, ASM Press, Washington DC, 10th edition.

Apewokin SN, WM Geisler, and LH Bachmann, 2010, Spontaneous Resolution of Extragenital Chlamydial and Gonococcal Infections Prior to Therapy, Sex Transm Dis, 37:343-344.

Aplasca de los Reyes MR, V Pato-Mesola, JD Klausner, et al., 2001, A Randomized Trial of Ciprofloxacin versus Cefixime for Treatment of Gonorrhea after Rapid Emergence of Gonococcal Ciprofloxacin Resistance in The Philippines, Clin Infect Dis, 32:1313-1318.

Bolan GA, PF Sparling, and JN Wasserheit, 2012, The Emerging Threat of Untreatable Gonococcal Infection, N Engl J Med, 366(6):485-487.

Del Rio C, G Hall, K Holmes, et al., 2012, Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections, Morbidity and Mortality Weekly Report, 61:590-594.

DerSimonian R and N Laird, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7:177-188.

Handsfield HH, TO Lipman, JP Harnisch, E Tronca, and KK Holmes, 1974, Asymptomatic Gonorrhea in Men. Diagnosis, Natural Course, Prevalence and Significance, N Engl J Med, 290(3):117-123.

Hook EW 3rd, FN Judson, MS Verdon, JM Ehret, and HH Handsfield, 1986, Comparative Study of Cefoperazone and Spectinomycin for Treatment of Uncomplicated Gonorrhea in Men, Antimicrob Agents Chemother, 30(4):619-621.

Hutt DM and FN Judson, 1986, Epidemiology and Treatment of Oropharyngeal Gonorrhea, Ann Intern Med, 104:655-658.

Kirkcaldy RD, GA Bolan, and JN Wasserheit, 2013, Cephalosporin-Resistant Gonorrhea in North America, JAMA, 309(2):185-187.

Sandberg ET, PS Pegram, RE Roddy, et al., 1986, Dose Ranging Study of Cefpimizole (U-63196E) for Treatment of Uncomplicated Gonorrhea in Men, Antimicrob Agents Chemother, 29(5):849-851.

Satterwhite CL, E Torrone, E Mietes, et al., 2013, Sexually Transmitted Infections Among US Women and Men: Prevalence and Incidence Estimates, 2008, Sex Transm Dis, 40(3):187-193.

APPENDIX: JUSTIFICATION FOR NONINFERIORITY MARGIN

A search of the historical literature identified three prospective, randomized, and blinded trials in which effective therapy was compared to ineffective or less effective therapy. Because the ineffective or less effective therapy used for comparison probably had some overall effect, these trials gave a conservative estimate of the effect of a fully effective therapy. Table 1 outlines each trial and the results of a random effects meta-analysis.

Table 1. Prospective, Randomized, Blinded Trials in Uncomplicated Gonorrhea

Trial Publication	Population (Micro-ITT; Missing = Failure)	Design	Endpoint (Success = Negative Culture)	Results in Effective Therapy Group	Results in Ineffective/Less Effective Therapy Group	Difference (95% CI)
Aplasca de los Reyes, Pato-Mesola, et al. 2001	Females, cervicitis	Prospective, double-blind	Repeat culture at 4-7 days	Cefixime (susceptible) 25/28 (89.0%)	Ciprofloxacin (resistance identified) 48/77 (62.3%)	27% (11.2%, 42.7%)
Hook 3rd, Judson, et al. 1986	Males, anogenital infection (most urethritis)	Randomized, dose-response single-blind, phase 2 trial	Repeat cultures 3-8 days post-Rx	Cefoperazone higher dose 61/68 (89.7%)	Cefoperazone lower dose 36/48 (75%)	14.7% (1%, 28.9%)
Sandberg, Pegram, et al. 1986	Males, anogenital or pharyngeal infection, (most urethritis)	Randomized, dose-response, single-blind, phase 2 trial	Return 3-7 days for repeat culture	Cefpimizole highest dose 23/25 (92%)	Cefpimizole lowest dose 18/27 (66.7%)	25.3% (5%, 46.1%)
Random effects meta-analysis (DerSimonian and Laird 1986): Risk difference 21.3%, lower bound of the two-sided 95% CI = 11.9%						

As noted above, these trials gave a conservative estimate of the treatment effect based on a negative culture for *N. gonorrhoeae* at approximately 3 to 8 days following administration of a single dose of an antibacterial drug. The lower bound of the two-sided 95 percent CI for the risk difference was 11.9 percent.

Three other studies provided evidence that a treatment difference of 11.9 percent is a conservative estimate of the effect of an antibacterial drug in the treatment of uncomplicated gonorrhea. Patients who were not treated for oropharyngeal gonococcal infection at a baseline visit (and were later identified by a positive culture at baseline) had spontaneous resolution rates of approximately 10 percent, 20 percent, and 50 percent when repeat culture of the pharynx was obtained at day 3, day 5, and day 7, respectively (Hutt and Judson 1986). Untreated patients with oropharyngeal gonorrhea showed spontaneous resolution in 3 out of 11 (27 percent) patients on repeat cultures obtained at an average of 11 days, whereas none of the 6 patients with untreated rectal gonorrhea showed spontaneous resolution (Apewokin, Geisler, et al. 2010). An assessment of the natural course of asymptomatic urethral gonorrhea demonstrated that 5 out of 28 (18 percent) untreated patients had spontaneous resolution (Handsfield, Lipman, et al. 1974).

If spontaneous resolution rates for uncomplicated gonorrhea were used as a comparison to effective treatment, the estimated treatment difference would be much larger than 11.9 percent. Therefore, an effectiveness margin of the active-controlled drug relative to placebo (M_1) defined at approximately 11.9 percent is a conservative estimate. In general, a noninferiority margin (M_2) selected at 10 percent is supported by the historical literature using an endpoint of the establishment of a negative culture for *N. gonorrhoeae* at approximately 3 to 7 days following treatment.