
Guidance for Industry Uncomplicated Gonorrhea: Developing Drugs for Treatment

DRAFT GUIDANCE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)**

**June 2014
Clinical/Antimicrobial**

Guidance for Industry Uncomplicated Gonorrhea: Developing Drugs for Treatment

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TABLE OF CONTENTS

- I. INTRODUCTION..... 1**
- II. BACKGROUND 2**
- III. DEVELOPMENT PROGRAM..... 2**
 - A. General Considerations2**
 - 1. Early Phase Clinical Development Considerations2*
 - 2. Drug Development Population.....2*
 - 3. Efficacy Considerations3*
 - 4. Safety Considerations.....3*
 - B. Specific Efficacy Trial Considerations3**
 - 1. Trial Design, Populations, and Entry Criteria.....3*
 - 2. General Exclusion Criteria4*
 - 3. Clinical Microbiology Considerations4*
 - 4. Randomization, Stratification, and Blinding4*
 - 5. Specific Populations4*
 - 6. Dose Selection5*
 - 7. Choice of Comparators and Concomitant Therapy5*
 - 8. Efficacy Endpoint5*
 - 9. Secondary Endpoints.....6*
 - 10. Trial Procedures and Timing of Assessments.....6*
 - 11. Statistical Considerations6*
 - a. Analysis populations.....6*
 - b. Noninferiority margins7*
 - c. Sample size7*
 - C. Other Considerations7**
 - 1. Pharmacokinetic/Pharmacodynamic Considerations7*
 - 2. Investigational Drugs With Activity Against N. gonorrhoeae and C. trachomatis8*
 - 3. Labeling Considerations8*
- REFERENCES..... 9**
- APPENDIX: JUSTIFICATION FOR NONINFERIORITY MARGIN..... 10**

1 **Guidance for Industry¹**
2 **Uncomplicated Gonorrhea: Developing Drugs for Treatment**
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7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
13

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17 **I. INTRODUCTION**
18

19 The purpose of this guidance is to assist sponsors in the clinical development of drugs for the
20 treatment of uncomplicated gonorrhea.² Specifically, this guidance addresses the Food and Drug
21 Administration's (FDA's) current thinking regarding the overall development program and
22 clinical trial designs for antibacterial drugs for the treatment of uncomplicated gonorrhea. This
23 draft guidance is intended to serve as a focus for continued discussions among the Division of
24 Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.³
25

26 Treatment for uncomplicated gonorrhea for the past several decades has consisted of a single
27 dose of an antibacterial drug administered orally or intramuscularly and has achieved a high
28 proportion (95 percent or more) of successful outcomes at a test-of-cure-visit at about 1 week
29 after antibacterial drug administration. The current thinking described in this guidance is based
30 on substantial recent experience indicating that an antibacterial drug for the treatment of
31 uncomplicated gonorrhea will be administered as a single dose and will achieve microbiological
32 cure in a high proportion of patients.
33

34 This guidance does not contain discussion of the general issues of statistical analysis or clinical
35 trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

¹ This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) 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 uncomplicated gonorrhea.

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36 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*
37 *Trials*, respectively.⁴

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

44

45

II. BACKGROUND

46

47
48 Sexually transmitted infectious diseases are common in the United States. The Centers for
49 Disease Control and Prevention (CDC) estimated that approximately 820,000 incident cases of
50 gonorrhea occurred in 2008 in the United States (Satterwhite, Torrone, et al. 2013).

51 Antibacterial drug susceptibility profiles for *Neisseria gonorrhoeae* have continued to change to
52 more resistant isolates since the 1940s (Kirkcaldy, Bolan, et al. 2013; Del Rio, Hall, et al. 2012).
53 The potential for gonorrhea to become resistant to all currently available antibacterial drugs
54 (Bolan, Sparling, et al. 2012) highlights the need for the development of new antibacterial drugs
55 for the treatment of gonorrhea.

56

57

III. DEVELOPMENT PROGRAM

58

A. General Considerations

59

1. Early Phase Clinical Development Considerations

60

61
62 Sponsors involved in clinical development of an investigational antibacterial drug with in vitro
63 activity against *N. gonorrhoeae* are encouraged to consider drug development for the treatment
64 of uncomplicated gonorrhea.

65

2. Drug Development Population

66

67
68 The clinical development population should include patients with uncomplicated urethral,
69 cervical, rectal, or pharyngeal infections caused by *N. gonorrhoeae*.

70

71

72

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>.

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73 3. *Efficacy Considerations*

74
75 A single adequate and well-controlled noninferiority trial can provide evidence of effectiveness.⁵
76 Sponsors should discuss with FDA the independent confirmatory evidence that would provide
77 support for the evidence of effectiveness (e.g., the results of a trial in another infectious disease
78 indication). If treatment for uncomplicated gonorrhea is the only indication being sought for a
79 new investigational drug, in general we recommend two adequate and well-controlled trials;
80 however, in certain circumstances, a compelling outcome in a single trial might provide evidence
81 of effectiveness (e.g., showing superiority to a control drug in a planned noninferiority trial).

82 83 4. *Safety Considerations*

84
85 In general, we recommend a preapproval safety database of approximately 500 patients at the
86 proposed single dose. In general, the targeted duration of safety evaluation is approximately 3 to
87 7 days following the single dose administration.⁶ If the same or greater dose and duration of
88 therapy for treatment of uncomplicated gonorrhea were used in clinical trials for other infectious
89 disease indications, the safety information from clinical trials in other infectious disease
90 indications can contribute to the overall preapproval safety database.⁷ Sponsors should discuss
91 with FDA the appropriate size of the preapproval safety database during clinical development.
92 Sponsors should consider the option of unequal randomization in the efficacy trial (e.g., 2:1, 3:2)
93 as a means of augmenting the overall safety database.

94 95 **B. Specific Efficacy Trial Considerations**

96 97 1. *Trial Design, Populations, and Entry Criteria*

98
99 Trials should be prospective, randomized, and double-blind. The trial population should include
100 patients with evidence of uncomplicated gonorrhea (i.e., infection of the urethra, cervix, pharynx,
101 or rectum caused by *N. gonorrhoeae*). The entry criteria can be broad (e.g., including any
102 patient who has uncomplicated gonorrhea) or focused (e.g., patients who have urethritis or
103 cervicitis).

104
105 Some patients who have gonococcal infections are asymptomatic, and infection may be
106 established by tests during routine health care visits. Such patients can be included in clinical
107 trial populations.

108

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

⁶ 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.

⁷ See the guidance for industry *Premarketing Risk Assessment*.

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109 2. *General Exclusion Criteria*

110

111 The following patients should be excluded:

112

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

116

117 • Patients who have received any effective antibacterial therapy for the treatment of
118 gonorrhea

119

120 3. *Clinical Microbiology Considerations*

121

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

130

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

137

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

142

143 4. *Randomization, Stratification, and Blinding*

144

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

150

151 5. *Specific Populations*

152

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

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155
156 Sponsors should discuss drug development in the pediatric populations as early as is feasible. In
157 general, adolescents should be included during preapproval drug development. Adolescents can
158 be enrolled in phase 3 clinical trials, if appropriate. The Pediatric Research Equity Act (PREA),
159 as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA),
160 states that initial plans for the conduct of pediatric studies (referred to as an *initial pediatric study*
161 *plan*) must be submitted to FDA before the date on which required pediatric assessments are
162 submitted under PREA and no later than 60 days after the end-of-phase 2 meeting or such other
163 time as may be agreed upon by FDA and the sponsor.⁸

6. *Dose Selection*

164
165
166
167 Drugs for the treatment of uncomplicated gonorrhea generally should be administered as a single
168 dose. Sponsors should integrate findings from nonclinical studies, pharmacokinetics (PK), and
169 safety information from earlier stages of clinical development to select the dose or doses to be
170 evaluated in phase 3 clinical trials. The PK of the drug in specific populations (e.g., adolescent
171 patients, patients with renal or hepatic impairment) should be evaluated before initiation of phase
172 3 to determine whether dose adjustments are necessary. This evaluation may prevent the
173 exclusion of such patients from the phase 3 clinical trials.

7. *Choice of Comparators and Concomitant Therapy*

174
175
176
177 The active comparator in a phase 3 controlled trial should be an antibacterial drug that is
178 recommended for treatment of uncomplicated gonorrhea by authoritative scientific bodies based
179 on clinical evidence and that reflects current clinical practice.⁹

180
181 In general, treatment for *Chlamydia trachomatis* should be offered to all patients with a
182 diagnosis of uncomplicated gonorrhea (Del Rio, Hall, et al. 2012). Sponsors should discuss with
183 FDA the choice and timing of concomitant therapy if the investigational drug does not have
184 activity against *C. trachomatis*.

8. *Efficacy Endpoint*

185
186
187
188 The primary efficacy endpoint should be the establishment of a negative culture at the site or
189 sites of infection approximately 3 to 7 days after receipt of antibacterial drug therapy
190 (microbiological cure).

191

⁸ See PREA (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by FDASIA (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.

⁹ 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).

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192 9. *Secondary Endpoints*

193

194 Suggested secondary endpoints for the trial include the following:

195

196 • The results of NAAT following treatment

197

198 • Symptom resolution in the subgroup of patients who have baseline symptoms attributable
199 to uncomplicated gonorrhea¹⁰

200

201 10. *Trial Procedures and Timing of Assessments*

202

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

205

206 • Entry visit: Appropriate demographic information, history and physical examination
207 findings, a microbiological specimen, and safety laboratory tests should be collected at
208 this visit; patients should receive investigational antibacterial drug treatment at this visit.

209

210 • Visit at approximately 3 to 7 days after receipt of treatment: This visit should assess
211 microbiological cure using a microbiological specimen from the baseline infected site or
212 sites. Adverse effect information and, if appropriate, safety laboratory tests should also
213 be collected.

214

215 11. *Statistical Considerations*

216

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

220

221 a. *Analysis populations*

222

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

225

226 • Safety population — All patients who received the investigational drug during the trial

227

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

229

230 • Microbiological intent-to-treat (micro-ITT) population — All patients randomized who
231 have *N. gonorrhoeae* isolated on baseline culture

232

233 • Per-protocol population — Patients who follow important components of the trial

¹⁰ 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).

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- 235
- Per-protocol microbiologically evaluable population — Patients who follow important
236 components of the trial and have *N. gonorrhoeae* isolated on baseline culture (e.g.,
237 micro-ITT patients who follow important components of the trial)

238

239 The micro-ITT population should be considered the primary analysis population. In general,
240 sponsors should not consider analyses of the per-protocol populations as primary because after
241 randomization events or characteristics could potentially bias results in this population.
242 However, consistency of the results should be evaluated in all patient populations. Every attempt
243 should be made to limit the loss of patients from the trial such that the micro-ITT population and
244 per protocol microbiologically evaluable population are similar. The method for handling
245 missing data should be specified in the protocol.

246

b. Noninferiority margins

247

248
249 Noninferiority trials are informative only if there is reliable and reproducible evidence of
250 treatment effect for the active-controlled drug.¹¹ A noninferiority margin for the primary
251 efficacy endpoint of microbiological cure based on the demonstration of a negative culture result
252 is supported by historical data (see Appendix). Sponsors should discuss the selection of the
253 noninferiority margin with FDA in advance of trial initiation.

254

c. Sample size

255

256
257 An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately
258 190 patients per group based on a noninferiority margin selection of 10 percent and a
259 microbiological cure rate in the micro-ITT population of 90 percent in the control group (see
260 results from clinical trials in Table 1 of the Appendix). The trial should rule out a greater than 10
261 percent inferiority of the investigational drug to control drug (upper bound of the two-sided 95
262 percent confidence interval (CI) for the microbiological cure rate of control drug minus
263 investigational drug).

264

C. Other Considerations

265

1. Pharmacokinetic/Pharmacodynamic Considerations

266

267
268
269 The PK/pharmacodynamic (PD) characteristics of the drug should be evaluated in nonclinical
270 models (e.g., in vitro PK/PD models, animal models of infection). Nonclinical PK/PD
271 assessments should be integrated with findings from phase 1 PK assessments to help identify
272 appropriate dose and dosing regimens for evaluation in phase 2 and phase 3 clinical trials.
273 Collection of PK data in phase 2 trials can be used to explore dose-response relationships to
274 support dose selection for further evaluation in phase 3 trials.

275

¹¹ See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent FDA's current thinking on this topic.

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

277
278 Investigational drugs that have potential to treat both gonorrhea and chlamydia can have
279 concurrent clinical development programs. For example, a phase 3 trial can enroll patients with
280 clinical evidence of infection caused by *N. gonorrhoeae* and/or *C. trachomatis*. NAAT rapid
281 testing could direct patients into groups intended to evaluate treatment of gonorrhea, chlamydia,
282 or both. Sponsors should discuss a concurrent phase 3 development program with FDA.

283 284 3. *Labeling Considerations*

285
286 The labeled indication for the treatment of uncomplicated gonorrhea generally should reflect the
287 population for which there is substantial evidence of safety and effectiveness, which is usually
288 based on the types of patients evaluated in the clinical development program.

289
290 For example, if the clinical development program evaluated patients who had cervicitis or
291 urethritis (and patients with oropharyngeal or rectal gonorrhea were specifically excluded from
292 drug development), the indication should reflect that patient population:

293
294 *“Drug X is indicated for the treatment of uncomplicated gonorrhea (cervicitis/urethritis)*
295 *caused by susceptible strains of Neisseria gonorrhoeae.”*

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REFERENCES

298
299
300 Allen VG, L Mitterni, C Seah, et al., 2013, *Neisseria gonorrhoeae* Treatment Failure and
301 Susceptibility to Cefixime in Toronto, Canada, *JAMA*, 309(2):163-170.
302
303 American Society for Microbiology, 2011, *Manual of Clinical Microbiology*, ASM Press,
304 Washington DC, 10th edition.
305
306 Apewokin SN, WM Geisler, and LH Bachmann, 2010, Spontaneous Resolution of Extragenital
307 Chlamydial and Gonococcal Infections Prior to Therapy, *Sex Transm Dis*, 37:343-344.
308
309 Aplasca de los Reyes MR, V Pato-Mesola, JD Klausner, et al., 2001, A Randomized Trial of
310 Ciprofloxacin versus Cefixime for Treatment of Gonorrhea after Rapid Emergence of
311 Gonococcal Ciprofloxacin Resistance in The Philippines, *Clin Infect Dis*, 32:1313-1318.
312
313 Bolan GA, PF Sparling, and JN Wasserheit, 2012, The Emerging Threat of Untreatable
314 Gonococcal Infection, *N Engl J Med*, 366(6):485-487.
315
316 Del Rio C, G Hall, K Holmes, et al., 2012, Update to CDC's Sexually Transmitted Diseases
317 Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for
318 Gonococcal Infections, *Morbidity and Mortality Weekly Report*, 61:590-594.
319
320 DerSimonian R and N Laird, 1986, Meta-Analysis in Clinical Trials, *Control Clin Trials*, 7:177-
321 188.
322
323 Handsfield HH, TO Lipman, JP Harnisch, E Tronca, and KK Holmes, 1974, Asymptomatic
324 Gonorrhea in Men. Diagnosis, Natural Course, Prevalence and Significance, *N Engl J Med*,
325 290(3):117-123.
326
327 Hook EW 3rd, FN Judson, MS Verdon, JM Ehret, and HH Handsfield, 1986, Comparative Study
328 of Cefoperazone and Spectinomycin for Treatment of Uncomplicated Gonorrhea in Men,
329 *Antimicrob Agents Chemother*, 30(4):619-621.
330
331 Hutt DM and FN Judson, 1986, Epidemiology and Treatment of Oropharyngeal Gonorrhea, *Ann*
332 *Intern Med*, 104:655-658.
333
334 Kirkcaldy RD, GA Bolan, and JN Wasserheit, 2013, Cephalosporin-Resistant Gonorrhea in
335 North America, *JAMA*, 309(2):185-187.
336
337 Sandberg ET, PS Pegram, RE Roddy, et al., 1986, Dose Ranging Study of Cefpimizole (U-
338 63196E) for Treatment of Uncomplicated Gonorrhea in Men, *Antimicrob Agents Chemother*,
339 29(5):849-851.
340
341 Satterwhite CL, E Torrone, E Mietes, et al., 2013, Sexually Transmitted Infections Among US
342 Women and Men: Prevalence and Incidence Estimates, 2008, *Sex Transm Dis*, 40(3):187-193.
343

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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).

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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.