Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Joseph Toerner, MD, MPH, at 301-796-1400.

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

May 2018
Clinical/Antimicrobial

Uncomplicated Urinary Tract Infections: 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
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://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)

May 2018
Clinical/Antimicrobial

TABLE OF CONTENTS

Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 clinical development of drugs for the treatment of uncomplicated urinary tract infections (uUTIs).[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 drugs to support an indication for the treatment of uUTIs. 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]

We consider the treatment of uUTIs to be an indication distinct from the treatment of complicated urinary tract infections (cUTIs). This guidance addresses uUTIs only. The FDA issued a separate guidance on cUTIs.[4] 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.

[1] This guidance has been prepared by the Division of Anti-Infective Products (DAIP) 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 DAIP to discuss specific issues that arise during drug development.

[4] See the guidance for industry *Complicated Urinary Tract Infections: Developing Drugs for Treatment*. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

II. BACKGROUND

uUTI is defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on urine culture, accompanied by local signs and symptoms such as lower abdominal discomfort and dysuria. uUTIs, also referred to as *acute cystitis*, occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms, such as fever greater than 38 degrees Celsius or costo-vertebral angle pain. Urinary tract infections in males are characterized as cUTIs because these infections occur in association with urologic abnormalities such as instrumentation or bladder outlet obstruction (e.g., benign prostatic hypertrophy).

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Drug Development Population

The intended clinical trial population should be female patients with uUTIs.

2. Efficacy Considerations

Active-controlled trials designed for findings of superiority or noninferiority are potential options to evaluate antibacterial drugs for the treatment of uUTI. A treatment effect of antibacterial drug therapy for uUTI has been established (see the Appendix). Therefore, the noninferiority trial design is acceptable for demonstration of efficacy.

The treatment-delay placebo-controlled trial design allows for a finding of superiority of the investigational drug compared to placebo at a time point early in therapy, after which patients randomized to treatment delay receive antibacterial drug treatment. Sponsors interested in conducting a placebo-controlled trial should discuss trial design and safety issues with the FDA. All trial designs should provide appropriate provisions for patient safety.[5]

If a sponsor seeks an indication for an investigational drug for uUTI as the only indication, we recommend two adequate and well-controlled trials. A single adequate and well-controlled trial supported by other independent evidence, such as a trial in another infectious disease indication,

[5] For example, see the References section for references that include placebo-controlled or nonantibacterial-controlled trials in uUTI patients.

can provide evidence of effectiveness.[6] Sponsors should discuss with the FDA the other independent evidence that would be used to support the findings from a single trial in uUTI.

3. Safety Considerations

In general, we recommend a preapproval safety database of at least 800 patients at the proposed dose and duration for treatment. If the dose and duration of therapy used in clinical trials for other infectious disease indications were the same or greater than the dose and duration proposed for treatment of uUTI, the safety information from those clinical trials can be part of the overall preapproval safety database. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

4. Pharmacokinetic and Dose Selection Considerations

The pharmacokinetics of the drug should be determined, including its excretion in urine. Urinary concentrations of the drug are important when bacterial infection is limited to the lower urinary tract (i.e., uUTI). Drug concentrations in urine over time should be assessed during early stages of a clinical development program.

Phase 2 dose-ranging studies are recommended. Phase 2 studies should include assessment of blood and urine drug concentrations to explore exposure-response relationships for safety and efficacy. Consideration may be given to sparse blood sampling for drug exposure estimates in phase 3 trials.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Enrollment Criteria

Sponsors should conduct randomized, double-blind, controlled trials in female patients with uUTI, using a superiority or noninferiority design.

We recommend the following inclusion and exclusion criteria:

- Patients should be adult females and, if appropriate, adolescent females with evidence of pyuria (see section III.B.2., Clinical Microbiology Considerations) and at least two of the following signs or symptoms of uUTI:

  – Dysuria
  – Urinary frequency
  – Urinary urgency
  – Suprapubic pain

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

- Patients with the following should be excluded:

  – Signs or symptoms of systemic illness such as fever greater than 38 degrees Celsius, shaking chills, or other clinical manifestations suggestive of cUTI

  – Treatment with other antibacterial drugs that are effective for treatment of the current uUTI

2. Clinical Microbiology Considerations

Before receipt of drug therapy, all patients should submit a urine specimen for culture and antimicrobial susceptibility testing.[7] A microscopic evaluation for pyuria (e.g., Gram stain) or dipstick analysis for leukocytes, nitrates, or a catalase test of the urine specimen should be performed. The urine specimen should be cultured using standard microbiology laboratory procedures. In general, a single species of bacteria on pure culture identified at 10^5 colony forming units per milliliter (CFU/mL) or greater should be considered a true bacterial pathogen,[8] and no growth of bacteria (or growth at a quantitation of less than 10^3 CFU/mL) should be considered a microbiologic success for a mid-stream clean-catch urine specimen (see section III.B.5., Efficacy Endpoints). Antimicrobial susceptibility testing of the isolates to the investigational drug and to other recommended antimicrobial drugs that may be used to treat uUTIs should be performed using standardized methods unless other in vitro susceptibility testing is justified.[9]

Development of new rapid diagnostic tests may facilitate future clinical trial design and potentially benefit patients by providing earlier diagnosis of causative organisms. Clinical trials of an investigational antibacterial drug for treatment of uUTI may provide an opportunity to contribute to the evaluation of a new diagnostic test. Sponsors interested in the development of a new rapid diagnostic test should discuss this opportunity with the FDA.

3. Specific Populations

Patients across a wide age range, including geriatric patients,[10] should be enrolled in the trials. Patients with hepatic impairment can be enrolled in phase 3 trials provided the pharmacokinetics

[7] Proper methods of urine specimen collection for analysis and culture are important enrollment considerations for clinical trials. See, for example, publications from the American Society for Microbiology, such as American Society for Microbiology, 2010, Clinical Microbiology Procedures Handbook, 3rd Edition, or a more recent edition; and American Society for Microbiology, 2009, Cumitech 2C: Laboratory Diagnosis of Urinary Tract Infections, coordinating editor SE Sharp, or a more recent edition.

[8] Sponsors should prespecify in the protocol how patients who have more than one bacterial species (isolated on a baseline urine culture) will be handled in the efficacy analysis.

[9] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

[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*.

of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

Sponsors are encouraged to begin discussions about their pediatric clinical development plans as early as is feasible because pediatric studies under section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), if applicable, 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 the FDA and the sponsor.[11] Adolescents can be included in phase 3 safety and efficacy trials, if appropriate.

Given the different clinical considerations regarding urinary tract infections in pregnant patients (Gupta et al. 2011), sponsors should discuss with the FDA if the investigational drug is being considered for use in pregnant patients who may have the potential to benefit from the investigational drug.

4. Choice of Comparators

In general, sponsors should use an active comparator that is considered standard of care for treatment of uUTI in the United States for this indication. The active comparator generally should be approved by the FDA for treatment of uUTI. However, when evaluating the current standard of care, we consider recommendations by authoritative scientific bodies (e.g., Infectious Diseases Society of America) based on clinical evidence and other reliable information that reflects current clinical practice. For a noninferiority trial, it is important that the analysis population includes only patients for whom the bacterial pathogen is fully susceptible to the active control drug on in vitro susceptibility testing.

5. Efficacy Endpoints

The following subsections describe the recommended primary efficacy endpoint and secondary endpoints.

a. Primary efficacy endpoint

The primary efficacy endpoint should be based on a responder outcome of clinical and microbiologic response.

- **Clinical and microbiologic response:** Resolution of the symptoms of uUTI (see section III.B.1., Clinical Trial Designs, Populations, and Enrollment Criteria) present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry is reduced to fewer than 10^3 CFU/mL on urine culture (microbiologic response) assessed at a fixed time point after randomization that is based on the duration of investigational antibacterial drug therapy and half-life of the investigational drug.

[11] See section 505B of the FD&C Act and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

- **Clinical or microbiologic failure:** Patients who did not meet the definition of *clinical and microbiologic response* (see above) or who died during the trial.

b. Efficacy endpoints for a finding of superiority

Sponsors can use the primary efficacy endpoint discussed in section III.B.5.a., Primary efficacy endpoint, or discuss other endpoints and clinical trial designs for superiority with the FDA, including designs that incorporate a delayed treatment group with standard or approved therapies (see section III.B.4., Choice of Comparators).

c. Secondary endpoints

Patients should be evaluated for continued resolution of symptoms and microbiologic success at a fixed time point approximately 21 to 28 days following randomization. This assessment helps to evaluate sustained microbiologic success *and* resolution of all clinical symptoms of uUTI (a responder outcome) as a secondary endpoint. Sponsors also should evaluate the clinical and microbiologic responses separately at each fixed time point assessment as secondary endpoints.

6. Trial Procedures and Timing of Assessments

a. Entry visit

Sponsors should collect baseline demographic and clinical information at the entry visit and include clinical signs and symptoms, microbiologic specimens (Gram stain and culture of urine; blood culture), and laboratory tests, as appropriate.

b. On-therapy and end-of-therapy visits

Patients should be evaluated at least once during therapy or at the end of prescribed therapy. Clinical and laboratory assessments for safety should be performed as appropriate. If the investigational drug needs to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol.

c. Post-treatment visits

The responder endpoint should be evaluated at a fixed time point after randomization that is based on the duration of investigational antibacterial drug therapy and half-life of the investigational drug. Patients should be evaluated by history and physical examination for adverse reactions. Symptoms of uUTI should be assessed at this visit and a urine specimen should be obtained for microscopic examination and culture. An assessment for the maintenance of clinical and microbiologic response should occur at approximately 21 to 28 days after randomization.

7. Statistical Considerations

In general, sponsors should develop a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis is usually based on the difference in the proportions of patients achieving a successful response.

a. Analysis populations

The following definitions apply to various analysis populations in uUTI clinical trials:

- **Intent-to-treat (ITT) population:** All patients who were randomized.

- **The microbiological intent-to-treat population (micro-ITT population):** Randomized patients who did not have growth of a bacterial pathogen on culture of urine at baseline should be excluded from this population. For a noninferiority trial, the micro-ITT population should include patients who have growth of bacterial pathogens on culture of urine at baseline demonstrating susceptibility to the active control drug. Patients should not be excluded from this population based on events that occurred post-randomization (e.g., loss to follow-up).

- **Clinically evaluable population:** Patients who meet the definition of the ITT population and who follow important components of the trial as specified in the protocol.

- **Microbiologically evaluable population:** Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

- **Safety population:** All patients who received at least one dose of the drug during the trial.

The micro-ITT population should be considered the primary analysis population for a noninferiority trial. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations provided in the final report.

b. Noninferiority margins

Noninferiority trials can be an appropriate trial design if there is reliable and reproducible evidence of a treatment effect for the comparator drug.[12] For a uUTI trial, a noninferiority margin of 10 percent is supported by historical evidence (see the Appendix).

[12] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.

c. Sample size

An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately 310 patients per group in the micro-ITT population. This sample size is based on a noninferiority margin of 10 percent, a clinical success rate in the micro-ITT population of 80 percent in the treatment and control groups, a two-sided $\alpha = 0.05$ statistical significance level, and 90 percent power. Approximately 80 percent of patients should have a bacterial pathogen identified by baseline culture and belong to the micro-ITT population, thus approximately 388 patients per group may need to be included in the ITT population.

The sample size estimate for a treatment delay superiority trial with 1:1 randomization is approximately 181 patients per group based on assumed success rates of 80 percent in the investigational group and 65 percent in the control group (e.g., placebo treatment delay), a two-sided $\alpha = 0.05$ statistical significance level, and 90 percent power.

8. Labeling Considerations

Generally, the labeled indication should be the treatment of uUTI caused by the specific bacteria identified in a sufficient number of patients in the clinical trials.

REFERENCES

Asbach HW, 1991, Single Dose Oral Administration of Cefixime 400mg in the Treatment of Acute Uncomplicated Cystitis and Gonorrhoea, Drugs, 42 Suppl 4:10–13.

Bleidorn J, I Gágyor, MM Kochen, K Wegscheider, and E Hummers-Pradier, 2010, Symptomatic Treatment (Ibuprofen) or Antibiotics (Ciprofloxacin) for Uncomplicated Urinary Tract Infection? — Results of a Randomized Controlled Pilot Trial, BMC Med, 8:30.

Christiaens TC, M De Meyere, G Verschraegan, W Peersman, S Heytens, and JM De Maeseneer, 2002, Randomised Controlled Trial of Nitrofurantoin Versus Placebo in the Treatment of Uncomplicated Urinary Tract Infection in Adult Women, Br J Gen Pract, 52(482):729–734.

Dubi J, P Chappuis, and R Darioli, 1982, Treatment of Urinary Infection With a Single Dose of Co-Trimoxazole Compared With a Single Dose of Amoxicillin and a Placebo, Schweiz Med Wochenschr, 112(3):90–92.

Ferry SA, SE Holm, H Stenlund, R Lundholm, and TJ Monsen, 2007, Clinical and Bacteriological Outcome of Different Doses and Duration of Pivmecillinam Compared With Placebo Therapy of Uncomplicated Lower Urinary Tract Infection in Women: The LUTIW Project, Scand J Prim Health Care, 25(1):49–57.

Gágyor I, J Bleidorn, MM Kochen G Schmiemann, K Wegscheider, and E Hummers-Pradier, 2015, Ibuprofen Versus Fosfomycin for Complicated Urinary Tract Infection in Women: Randomized Controlled Trial, BMJ, 351:h6544.

Gupta K, TM Hooton, KG Naber, B Wullt, R Colgan, LG Miller, GJ Moran, LE Nicolle, R Raz, AJ Schaeffer, and DE Soper, 2011, International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin Infect Dis, 52(5):e103–e120.

Vik I, M Bollestad, N Grude, A Bærheim, S Mölstad, L Bjerrum, and M Lindbæk, 2014, Ibuprofen Versus Mecillinam for Uncomplicated Cystitis — A Randomized Controlled Trial Study Protocol, BMC Infectious Diseases,14:693.

APPENDIX: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR UNCOMPLICATED URINARY TRACT INFECTIONS

We identified two trials of uncomplicated urinary tract infection (uUTI) that used a placebo control, assessed a combined clinical and microbiological eradication outcome and were published in the English language (Asbach 1991; Ferry et al. 2007). Young adult women with symptoms such as dysuria and urinary frequency and/or urgency and a baseline urine culture positive for a bacterial pathogen (e.g., growth of bacteria at a quantitation of greater than 10^5 colony forming units per milliliter (CFU/mL)) were enrolled in these trials. The responder efficacy endpoint of both resolution of symptoms (clinical resolution) and microbiological eradication of the bacterial pathogen from urine (bacterial pathogen found at trial entry is reduced to fewer than 10^3 CFU/mL on follow-up urine culture) was evaluated in these two trials (Table 1).

Table 1: Clinical Resolution Plus Microbiological Eradication Outcome Assessment

Study Name (first author)	Timing of Outcome Assessment	Antibacterial Group Responder Rate	Control Group Responder Rate	Difference	95% CI*
Asbach	Days 14-17 post therapy	Oral cefixime (400 mg single dose) **50/57 (88%)**	Placebo **5/19 (26%)**	61.4%	36.3% to 86.5%
Ferry	Days 8-10	Oral pivmecillinam (pooled groups given 200 mg TID* x7 days, 200 mg BID* x7 days, or 400 mg BID x3 days) **374/657 (57%)**	Placebo **30/227 (13%)**	43.7%	37.5% to 49.2%
Random effects meta-analysis				49.4%	33.2% to 65.6%

* CI = confidence interval; TID = *ter in die* or three times per day; BID = *bis in die* or two times per day

An estimate for the treatment difference for the responder efficacy endpoint of clinical resolution plus microbiological eradication is approximately 33 percent (the lower bound of the two-sided 95 percent confidence interval from Table 1). Because of the differences between the point estimate antibacterial group responder rates and what might be expected in prospective noninferiority trials, we propose a 50 percent discount of the treatment effect to account for uncertainties and generalizability issues when translating the historical treatment effect to the effect of a current active control, as recommended in the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*.[1] We propose an estimated treatment difference (M_1) of approximately 16 percent. Considering preservation of the treatment effect, we recommend a clinically acceptable noninferiority margin (M_2) of 10 percent.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We identified five additional published prospective and controlled trials of uUTI. Four of the trials describe results that are supportive of the treatment effect of an antibacterial drug for uUTI. These five trials were not included in the meta-analysis above for the responder endpoint for the following reasons.

1. One trial (Bleidorn et al. 2010) compared antibacterial drug treatment to ibuprofen. Ibuprofen appeared to influence symptom resolution as compared to ciprofloxacin, thus the trial did not show a significant difference between treatment groups for symptom resolution at Days 4 and 7. There appeared to be an advantage for the antibacterial group for the microbiological eradication endpoint on Day 7 (72 percent eradication in the ciprofloxacin group compared to 49 percent in the ibuprofen group), but this difference was not statistically significant.

2. A second trial (Christiaens et al. 2002) evaluated clinical and microbiologic response separately, which showed significant differences in favor of the antibacterial drug group over placebo on Days 3 and 7 for either endpoint. However, this trial was not included in the analysis because patient level data were not available to assess an individual's outcome on the combined responder endpoint.

3. A third trial (Gágyor et al. 2015) enrolled patients that presented to an outpatient clinic with signs and symptoms of uUTI, regardless of whether a baseline urine culture demonstrated a bacterial pathogen. Furthermore, there were no outcome data on microbiological eradication because the trial did not evaluate urine cultures at a follow-up visit. A greater proportion of women achieved a statistically significant resolution of symptoms at Day 7 in the fosfomycin group compared to the ibuprofen group (82 percent for fosfomycin group and 70 percent for the ibuprofen group).

4. A fourth trial (Dubi et al. 1982) was not published in the English language and approximately 25 percent of the patients enrolled in this trial had only a positive urine culture with no symptoms of uUTI (i.e., women with asymptomatic bacteriuria). This trial showed a statistically significant difference in favor of the antibacterial drug on the responder endpoint compared to placebo (70 percent versus 44 percent, respectively), although these results were likely driven by the microbiological eradication outcome measure due to some patients not having symptoms at baseline.

5. Another trial enrolling women with uUTI, randomized to receive an antibacterial drug or ibuprofen, has been described in the literature but results have not yet been published for potential consideration in the noninferiority justification (Vik 2014).