
Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

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

**October 2013
Clinical/Antimicrobial**

Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment

Additional copies are available from:

*Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration*

*10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002*

Tel: 301-796-3400; Fax: 301-847-8714; E-mail: 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)**

**October 2013
Clinical/Antimicrobial**

TABLE OF CONTENTS

I. INTRODUCTION..... 1

II. BACKGROUND 2

III. DEVELOPMENT PROGRAM..... 2

A. General Considerations2

 1. *Definitions of Acute Bacterial Skin and Skin Structure Infection* 2

 2. *Efficacy Considerations* 3

 3. *Safety Considerations* 3

B. Specific Efficacy Trial Considerations 4

 1. *Clinical Trial Designs, Populations, and Entry Criteria* 4

 2. *General Exclusion Criteria*..... 4

 3. *Clinical Microbiology Considerations* 4

 4. *Prior Antibacterial Drug Therapy* 5

 5. *Concurrent Antibacterial Drug Therapy* 6

 6. *Adjunctive Therapy* 6

 7. *Efficacy Endpoints and Timing of Assessments* 6

 a. *Primary efficacy endpoint of lesion response at 48 to 72 hours* 6

 b. *Secondary endpoint considerations*..... 7

 8. *Trial Procedures and Timing of Assessments* 7

 a. *Entry visit*..... 7

 b. *On-therapy visit at approximately 48 to 72 hours*..... 7

 c. *End-of-therapy visit* 7

 d. *After-therapy visit*..... 7

 9. *Statistical Considerations* 8

 a. *Analysis populations* 8

 b. *Noninferiority margins*..... 8

 c. *Sample size* 9

 10. *Specific Populations* 9

C. Other Considerations..... 9

 1. *Pharmacokinetic/Pharmacodynamic Considerations*..... 9

 2. *Dose Selection and Formulation* 10

 3. *Labeling Considerations*..... 10

REFERENCES..... 11

APPENDIX: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS 13

Guidance for Industry¹
Acute Bacterial Skin and Skin Structure Infections:
Developing Drugs for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial skin and skin structure infections (ABSSSI).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 systemic drugs to support an indication for the treatment of ABSSSI. This guidance defines ABSSSI as cellulitis/erysipelas, wound infection, and major cutaneous abscess.

This guidance does not address less serious skin infections, such as impetigo and minor cutaneous abscess,³ as well as infections needing more complex treatment regimens, such as infections resulting from animal or human bites, necrotizing fasciitis, diabetic foot infection, decubitus ulcer infection, myonecrosis, and ecthyma gangrenosum. Sponsors interested in development of drugs for treatment of skin infections not covered in this guidance should discuss clinical development plans with the FDA.

This guidance also 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*

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 Sponsors interested in the development of drugs for treatment of impetigo or minor cutaneous abscess should discuss their development plans with the FDA. In general, such trials should be designed for a finding of superiority; see the transcripts of the discussion at the November 18, 2008, Anti-Infective Drugs Advisory Committee (AIDAC) meeting.

Contains Nonbinding Recommendations

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

FDA's guidance documents, including this guidance, 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

This guidance provides information to assist sponsors developing drugs for the treatment of skin infections that are termed *acute bacterial skin and skin structure infections*.⁵ ABSSSI include cellulitis/erysipelas, wound infection, and major cutaneous abscess and have a minimum lesion surface area of approximately 75 cm². Common bacterial pathogens causing ABSSSI are *Streptococcus pyogenes* and *Staphylococcus aureus* including methicillin-resistant *S. aureus*. Less common causes include other *Streptococcus* species, *Enterococcus faecalis*, or Gram-negative bacteria.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definitions of Acute Bacterial Skin and Skin Structure Infection

An ABSSSI is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm² (lesion size measured by the area of redness, edema, or induration).⁶ The minimum area of involvement of 75 cm² is chosen to select patients with acute bacterial skin infections for which a reliable control drug treatment effect can be estimated, given that most drugs for ABSSSI will be

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 Public discussions, including the AIDAC meeting on November 18, 2008, discussed the previous characterization of skin and skin structure infections into two broad categories: (1) uncomplicated skin and skin structure infections; and (2) complicated skin and skin structure infections. In addition to suggestions for re-characterizing categories of skin and skin structure infections, noninferiority clinical trial designs and endpoints were discussed. Transcripts and briefing information from the AIDAC meeting can be found at the FDA Web site at <http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective>.

⁶ For areas of ABSSSI that involve certain body surface sites, such as the face, or for young children when it is appropriate to enroll them in a phase 3 clinical trial, sponsors can discuss with the FDA the proposed definitions of ABSSSI that are based on a surface area smaller than 75 cm².

Contains Nonbinding Recommendations

studied using noninferiority trial designs.⁷ A sufficiently large lesion size also differentiates between *minor cutaneous abscess* (smaller than approximately 75 cm²) and *major cutaneous abscess* (greater than approximately 75 cm²). This distinction is important because there appears to be insufficient information to reliably estimate a quantitative treatment effect of an antibacterial drug for patients who have surgical incision and drainage for a minor cutaneous abscess (Duong, Markwell, et al. 2010; Lee, Rios, et al. 2004; Llera and Levy 1985; Rajerdran, Young, et al. 2007).

Patients with the following infection types can be enrolled in ABSSSI clinical trials:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration
- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration
- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

The method of measuring lesion size should be the same across all trial sites. Methods to assess lesion size include, but are not limited to, the following: (1) manual measurement of length multiplied by perpendicular width; (2) digital planimetry; and (3) computer-assisted tracings.

2. Efficacy Considerations

Noninferiority trials are interpretable and acceptable to support approval of a drug for an indication of the treatment of ABSSSI. A showing of superiority to an effective control is also readily interpretable and would be acceptable.

If an indication for the treatment of ABSSSI is the sole indication for which the drug has been, or is being, developed, then two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness. A single adequate and well-controlled trial supported by other independent evidence, such as a trial in another infectious disease indication (e.g., treatment of community-acquired bacterial pneumonia), could also provide evidence of effectiveness in the treatment of ABSSSI.⁸ Sponsors should discuss with the FDA other independent confirmation that would be used to support the findings from a single trial in ABSSSI.

3. Safety Considerations

In general, we recommend a preapproval safety database of approximately 700 patients or more. If the same or greater dose and duration of therapy for the treatment of ABSSSI were used in

⁷ See the Appendix and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

⁸ See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

Contains Nonbinding Recommendations

clinical trials for other infectious disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database. For new drugs that have an important clinical benefit compared to existing therapies, depending on the benefit demonstrated, a smaller preapproval safety database may be appropriate. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Entry Criteria

The clinical trial population for efficacy trials should include male and female patients with a mixture of the ABSSSI disease entities (e.g., cellulitis/erysipelas, wound infection, major cutaneous abscess) described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection. Because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses, patients with major cutaneous abscesses should not comprise more than 30 percent of the clinical trial population.

2. General Exclusion Criteria

Recommended general exclusion criteria include the following:

- Patients with medical conditions that would alter the interpretation of a primary endpoint (e.g., patients with neutropenia)
- Patients with suspected or confirmed osteomyelitis
- Patients with suspected or confirmed septic arthritis
- Patients who have received more than 24 hours of effective antibacterial drug therapy for treatment of the current episode of ABSSSI (see section III.B.4., Prior Antibacterial Drug Therapy)

3. Clinical Microbiology Considerations

Sponsors should obtain an adequate clinical specimen for microbiologic evaluation (e.g., pus from a wound or abscess; an aspirate from the leading edge of cellulitis), including culture, Gram stain, and in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods (e.g., American Society for Microbiology 2011). The specimen for microscopic evaluation and culture, as well as blood cultures from two separate venipuncture sites, should be obtained before administration of antibacterial therapy, if possible. This microbiological information is important for characterizing the underlying bacterial etiologies of ABSSSI.

Sponsors should save all isolates considered possible pathogens taken from patients enrolled in clinical trials in the event that additional testing of an isolate is needed (e.g., pulse field gel electrophoresis for strain identification).

Contains Nonbinding Recommendations

Rapid diagnostic tests can be used for enrichment of trial populations with specific infections. In addition, the clinical trial of an antibacterial drug may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors interested in the development of a new diagnostic test should discuss potential approaches with the FDA.

4. Prior Antibacterial Drug Therapy

Ideally, patients enrolled in an ABSSSI clinical trial would not have received prior antibacterial drug therapy because such therapy can have a number of potential consequences for a clinical trial. Prior antibacterial drug therapy could:

- Obscure any potential treatment differences between an investigational drug and control drug and therefore bias toward a finding of no difference (i.e., a bias toward noninferiority)
- Influence the evaluation of efficacy findings based on an endpoint earlier in therapy (48 to 72 hours)

However, a complete ban on prior antibacterial therapy could have adverse consequences, including:

- Exclusion of all patients who received prompt administration of antibacterial drug therapy because of the severity of their disease could result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; trial results could therefore be biased toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)
- Certain trial sites may not participate in the clinical trial because of concerns regarding standard-of-care treatment.

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of some patients who have received a single dose of a short-acting antibacterial drug within 24 hours of enrollment (e.g., ideally there would be few such patients, and they could be limited to 25 percent of the patient population). This would allow patients in the trial to receive prompt antibacterial drug therapy if that was clinically necessary, consistent with the standard of care. The results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy will be important to evaluate and the primary analysis can be stratified by prior therapy to assess the consistency of the results across the two subgroups (i.e., patients who received prior therapy and those who did not receive prior therapy).

There are other circumstances in which patients who received prior antibacterial drug therapy can be eligible for clinical trial entry:

Contains Nonbinding Recommendations

- Objective documentation of clinical progression of ABSSSI while on antibacterial drug therapy (i.e., not by patient history alone)
- The patient received an antibacterial drug for surgical prophylaxis and subsequently develops ABSSSI

5. Concurrent Antibacterial Drug Therapy

Ideally, concurrent antibacterial drug therapy should be avoided. However, certain patients with ABSSSI could receive additional empirical antibacterial drug treatment, preferably treatment that has no overlapping antibacterial activity with the investigational drug. For example, a patient who has a new diagnosis of ABSSSI while in the hospital (e.g., wound infection) might require empirical antibacterial drug therapy that treats both Gram-positive and Gram-negative bacterial pathogens; such a patient could enroll in a trial for an investigational drug that has only Gram-positive antibacterial activity, provided that the concurrent empirical antibacterial drug for Gram-negative treatment does not have overlapping Gram-positive antibacterial activity with the investigational drug.

6. Adjunctive Therapy

The following adjunctive therapy is often used in ABSSSI treatment:

- Daily dressing changes
- Use of topical solutions including nonspecific antimicrobial drugs such as povidone-iodine
- Debridement
- Hyperbaric oxygen treatments
- Surgical interventions planned at the initiation of treatment

Sponsors should specify which adjunctive therapies are to be permitted in the clinical trials. With proper blinding and randomization, both the investigational drug group and control group should have comparable use of these adjunctive therapies. Sponsors should analyze the clinical outcomes stratified by the presence or absence of adjunctive therapies (e.g., daily debridement). Topical treatments with specific antibacterial activity should not be used as adjunctive therapy in ABSSSI clinical trials.

7. Efficacy Endpoints and Timing of Assessments

- a. Primary efficacy endpoint of lesion response at 48 to 72 hours

Clinical response should be based on the percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. A

Contains Nonbinding Recommendations

clinical response in a patient generally is defined as a percent reduction in lesion size greater than or equal to 20 percent compared to baseline.⁹ Alternative metrics of lesion response should be discussed with the FDA before initiation of clinical trials.

b. Secondary endpoint considerations

Resolution of ABSSSI evaluated at 7 to 14 days after completion of therapy should be a secondary endpoint.

Refinement of the clinical outcome assessments in ABSSSI trials (e.g., lesion size measurements other than length times width) can be considered.¹⁰ In addition, symptoms, including pain, caused by ABSSSI can be important to evaluate.¹¹

8. *Trial Procedures and Timing of Assessments*

a. Entry visit

At this visit, sponsors should collect appropriate demographic information, history and physical examination findings, lesion size measurements, microbiological specimens, and safety laboratory tests.

b. On-therapy visit at approximately 48 to 72 hours

At this visit, sponsors should evaluate the lesion size in the same manner as at the entry visit, as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated.

c. End-of-therapy visit

At this visit, sponsors should evaluate the lesion size in the same manner as at the entry visit, as specified by the protocol. Safety and laboratory tests, as appropriate, should be evaluated. Assessment of whether discontinuation of antibacterial drug therapy is appropriate also can be made.

d. After-therapy visit

This visit should correspond to a visit within a window of approximately 7 to 14 days after the last day of therapy. Sponsors should assess the maintenance of clinical response and any new safety effects or safety laboratory tests, as appropriate, at this visit. A day-28 all-cause mortality assessment is recommended.

⁹ See, for example, Talbot, Powers, et al. 2012.

¹⁰ See Talbot, Powers, et al. 2012.

¹¹ For more information, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Contains Nonbinding Recommendations

9. *Statistical Considerations*

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis is based on the difference in the proportions of patients achieving a successful clinical response (e.g., at least a 20 percent reduction in the lesion size at 48 to 72 hours when compared to baseline). An exploratory analysis that compares clinical responses among patients who received prior antibacterial drug therapy and patients who did not receive prior antibacterial drug therapy should be considered.

a. Analysis populations

The definitions for the statistical analysis populations are provided as follows:

- Safety population — All patients who received at least one dose of drug during the trial.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Microbiological intent-to-treat (micro-ITT) population — All patients randomized to treatment who have a baseline bacterial pathogen known to cause ABSSSI. Patients should not be excluded from this population based upon events that occur after randomization (e.g., lost to follow-up).
- Per-protocol, clinically evaluable, or microbiologically evaluable populations — Patients who follow important components of the trial can then be defined as part of a per-protocol or other evaluable population (i.e., ITT patients who follow important components of the trial can be defined as the clinically evaluable population, or micro-ITT patients who follow important components of the trial can be defined as the microbiologically evaluable population).

In general, sponsors should consider the ITT population to be the primary analysis population because the definitions of ABSSSI described in section III.A.1., Definitions of Acute Bacterial Skin and Skin Structure Infection, are most consistent with bacterial infectious diseases even for cases in which purulent material is not easily obtained (e.g., cellulitis). For an antibacterial drug with targeted activity against a specific pathogen or class (e.g., a drug with antibacterial activity against Gram-negative pathogens), sponsors should discuss the appropriate analysis population with the FDA. Generally, it is not appropriate, as a scientific matter, to consider analyses of the per-protocol population as primary, because population membership is based on after randomization events or characteristics of patients. However, consistency of the results should be evaluated in all populations.

b. Noninferiority margins

A noninferiority margin of 10 percent for the primary efficacy endpoint based on a reduction in lesion size at 48 to 72 hours (defined in section III.B.7., Efficacy Endpoints and Timing of

Contains Nonbinding Recommendations

Assessments) is supported by the historical evidence (see the Appendix).¹² Sponsors should discuss the selection of a noninferiority margin with the FDA in advance of trial initiation, particularly for a proposed margin of greater than 10 percent or for a margin using an endpoint other than lesion response based on the reduction in lesion size (i.e., the proportion of patients achieving at least a 20 percent reduction in lesion size).

c. Sample size

An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately 310 patients per arm based on the following assumptions: (1) the noninferiority margin is selected at 10 percent; (2) the type I error is 0.05; (3) the type II error is 0.10 (90 percent power); and (4) 80 percent of patients achieve clinical success with the comparator drug.

10. Specific Populations

Sponsors should discuss drug development in the pediatric populations as early as is feasible. The Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration Safety and Innovation Act, states that initial plans for the conduct of pediatric studies (referred to as an *initial pediatric study plan*) shall be submitted to the FDA before the date on which required pediatric assessments are submitted under PREA and no later than: (1) 60 days after the end-of-phase 2 meeting; or (2) such other time as may be agreed upon by the Secretary and the applicant.¹³ In most situations, the course of the disease and the effects of therapy for ABSSSI are sufficiently similar in the adult and pediatric populations. Accordingly, under those circumstances, adult efficacy findings for drugs to treat ABSSSI may be extrapolated to the pediatric population. Pharmacokinetic (PK) and safety studies should be conducted to determine dosing in the pediatric population that provides exposure similar to exposure that is effective in adults and safety information at the identified dose(s). Drug development programs should include a sufficient number of geriatric patients (e.g., older than 65 years of age and older than 75 years of age) to characterize safety and efficacy in this population.¹⁴

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

Sponsors should evaluate the PK/pharmacodynamic (PD) characteristics of the drug using in vitro models or animal models of infection. The results from nonclinical PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate

¹² See the draft guidance for industry *Non-Inferiority Clinical Trials*.

¹³ See PREA (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 112-114) 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.

¹⁴ 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*.

Contains Nonbinding Recommendations

dose and dosing regimens for evaluation in phase 2 and phase 3 clinical trials. Plasma drug concentrations should be determined from patients in phase 2 clinical trials. Using the plasma concentration data, the sponsor should assess the relationship between antibacterial PK/PD indices and observed clinical and microbiological outcomes. Antibacterial PK/PD indices include maximal unbound drug concentration [fC_{max}]/minimum inhibitory concentration (MIC) ratio, area under the unbound drug concentration-time curve [fAUC]/MIC ratio, or the percentage of the dosage interval that the unbound drug concentration exceeds the MIC [fT>MIC]. The evaluation of exposure-response relationships (efficacy and safety) in phase 2 helps determine the best dose for evaluation in phase 3 trials. PK samples can be obtained by various approaches, such as rich or sparse sampling obtained from specific subsets of patients and/or at specific trial sites.

Sponsors may want to consider obtaining plasma drug concentrations from patients in phase 3 clinical trials. The concentration data are most important when the population studied in phase 3 differs from the population studied in phase 2 (e.g., the phase 3 population has more severe illness). If phase 3 trials include a previously unstudied specific population, such as patients with renal or hepatic impairment, collection of plasma drug concentrations from those specific populations can aid in determining necessary dose adjustments. The concentration data can also help with the interpretation of any unexpected safety or efficacy findings.

2. Dose Selection and Formulation

Sponsors should integrate the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of target pathogens, safety and tolerability information from phase 1 trials, and safety and antibacterial activity information from phase 2 dose-ranging trials for purposes of selection of appropriate doses, dosing regimens, and duration of therapy to be evaluated in phase 3 clinical trials.

For drugs that only have an intravenous (IV) formulation available, we recommend that patients receive the IV formulation alone until the assessment of the primary efficacy endpoint (e.g., at 48 to 72 hours), without a switch to an FDA-approved oral antibacterial drug, if feasible.

For drugs that have both an IV and oral formulation, a switch to the oral drug may be appropriate before the primary efficacy outcome assessment at 48 to 72 hours provided that pharmacokinetics of the oral formulation have been evaluated to ensure adequate exposure and to determine an appropriate dosing regimen.

3. Labeling Considerations

The labeled indication for a drug approved for the treatment of ABSSSI should be for the treatment of ABSSSI caused by specific bacteria identified in patients in the clinical trials. For example:

“Drug X is indicated for the treatment of acute bacterial skin and skin structure infections due to ... [list genus and species of bacteria].”

Contains Nonbinding Recommendations

REFERENCES

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

Corwin P, Toop L, McGoech G et al., 2005, Randomized Controlled Trial of Intravenous Antibiotic Treatment for Cellulitis at Home Compared With Hospital, *BMJ*, 330(7483):129. (Epub 2004 Dec 16.)

Duong M, Markwell S, Peter J, and Barenkamp S, 2010, Randomized, Controlled Trial of Antibiotics in the Management of Community-Acquired Skin Abscesses in the Pediatric Patient, *Ann Emerg Med*, 55(5):401-7.

Florey ME and Williams RE, 1944, Hand Infections Treated With Penicillin, *Lancet*, January 15;1(6281):73-81.

Lavender HJ and Goldman L, 1935, Evaluation and Comparison of Specific Antiserum and Ultraviolet Therapy, *JAMA*, 105:401-403.

Lee MC, Rios AM, Aten MF et al., 2004, Management and Outcome of Children With Skin and Soft Tissue Abscesses Caused By Community-Acquired Methicillin-Resistant *Staphylococcus aureus*, *Pediatric Infectious Disease Journal*, 23:123-127.

Llera JL and Levy RC, 1985, Treatment of Cutaneous Abscess: A Double-Blind Clinical Study, *Annals of Emergency Medicine*, 14:15-19.

Rajendran PM, Young D, Maurer T et al., 2007, Randomized, Double-Blind Placebo-Controlled Trial of Cephalexin for Treatment of Uncomplicated Skin Abscesses in a Population at Risk for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infection, *Antimicrob Agents and Chemother*, 51:4044-4048.

Skinner D and Keefer CS, 1941, Significance of Bacteremia Caused By *Staphylococcus aureus*, *Archives of Internal Medicine*, 68:851-875.

Snodgrass WR and Anderson T, 1937(a), Prontosil in the Treatment of Erysipelas; A Controlled Series of 312 Cases, *BMJ*, 2:101-104 (July 17).

Snodgrass WR and Anderson T, 1937(b), Sulfanilamide in the Treatment of Erysipelas; A Controlled Series of 270 Cases, *BMJ*, 2:1167-1159 (Dec 11).

Spellberg B, Talbot GH, Boucher HW, Bradley JS, Gilbert D, Scheld WM, Edwards J, Bartlett JG, and Antimicrobial Availability Task Force of the Infectious Diseases Society of America, 2009, Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Justification of Noninferiority Margins in the Absence of Placebo-Controlled Trials, *Clin Infect Dis*, Aug 1;49(3):383-91.

Contains Nonbinding Recommendations

Sutherland DS and Day FM, 1935, The Ultra-Violet Light Treatment of Erysipelas, The Medical Officer, Nov 2;185-186.

Symmers D, 1928, The Antitoxin Treatment of Erysipelas, Journal of the American Medical Association, 91(5):535-538.

Talbot GH, Powers JH, Fleming TR et al., 2012, Progress on Developing Endpoints for Registrational Clinical Trials of Community-Acquired Pneumonia and Acute Bacterial Skin and Skin Structure Infections: Update From the Biomarkers Consortium of the Foundation for the National Institutes of Health, Clin Infect Dis;55:1114-1121.

Titus NE, 1934, The Treatment of Erysipelas By Ultra-Violet Light, Br. J of Physical Medicine, 150-152.

Ude WH and Platou ES, 1930, Erysipelas; A Comparative Study of the More Recent Methods of Treatment, JAMA, 95(1):1-4.

Ude WH, 1931, Erysipelas; Further Comparative Studies of the More Recent Methods of Treatment, Archives of Physical Therapy, x-ray, radium, 16-18.

**APPENDIX:
JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR ACUTE BACTERIAL
SKIN AND SKIN STRUCTURE INFECTIONS**

Background

The first step in the consideration for a noninferiority trial design is determining the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M_1). This margin is based on evidence from previously conducted trials using reliable efficacy endpoints.¹⁵ For ABSSSI, there were no placebo-controlled trials reported in the historical literature. However, two controlled trials evaluated antibacterial drugs versus nonantibacterial treatments in patients with cellulitis/erysipelas. These two studies can be used to estimate the treatment difference for antibacterial drugs in the treatment of ABSSSI for the endpoint based on lesion size assessment.

Controlled Studies in Cellulitis/Erysipelas

Two controlled studies were identified in the scientific literature that compared outcomes in patients with cellulitis/erysipelas treated with an antibacterial drug versus ultraviolet (UV) light therapy (Snodgrass and Anderson 1937(a); Snodgrass and Anderson 1937(b)). During the 1930s, UV light was routinely used because previous studies published in the mid-1930s showed potential benefit in erysipelas when compared to other nonantibacterial therapies. UV light therapy was the control group in these studies.

Both studies enrolled patients with clinically documented erysipelas; however, the identification of a bacterial pathogen was not reported among study patients. Erysipelas and cellulitis can be difficult to distinguish clinically and physicians use both terms to describe skin infections of the upper dermis or subcutaneous tissues. We inferred that these two studies enrolled patients with cellulitis/erysipelas (ABSSSI) caused by either *S. pyogenes* or *S. aureus*.

In the first study (Snodgrass and Anderson 1937(a)), 312 patients admitted from May 1936 to February 1937 received one of four open-label treatments for erysipelas:

- UV light
- Prontosil (a sulfonamide antibacterial drug that is metabolized to sulphanilamide)
- UV light plus Prontosil
- Scarlet fever antitoxin

In the second study (Snodgrass and Anderson 1937(b)), 270 patients admitted from February 1937 to August 1937 received one of two open-label treatments for erysipelas:

- UV light
- Sulphanilamide (a sulfonamide antibacterial drug)

¹⁵ See the draft guidance for industry *Non-Inferiority Clinical Trials*.

Contains Nonbinding Recommendations

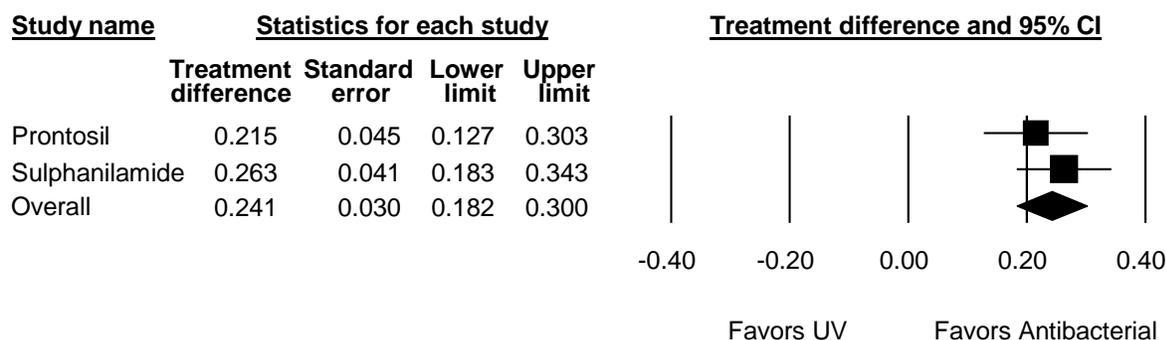
The efficacy endpoints were prespecified as clinical observations of whether the *lesion continues to spread*, the *temperature has become normal*, and the patient *continues in a toxic condition*. The largest treatment difference in lesion spread was the evaluation at 2 days; a smaller treatment difference was noted at day 3 and there was no difference in cessation of lesion spread at the day 4 time point. Because the authors described cessation of lesion spread at *day 0*, then at *day 1*, followed by *day 2*, and so forth, we assumed that the evaluation at day 2 represented an evaluation at approximately 48 to 72 hours of therapy (i.e., day 0 represented the assessment of the patients' lesions after some amount of time on therapy during the first day of hospitalization).

To estimate a treatment effect of an antibacterial drug, we evaluated the results of the cessation of spread of the lesion after 2 days of therapy. Table A provides summary information about the results of cessation of the spread of the lesion. Figure A shows the results of a random effects meta-analysis.

Table A. Results of Studies 1 and 2 as Reported in the Articles

	Study (a)		Study (b)	
	UV light	Prontosil	UV light	Sulphanilamide
N	104	106	135	135
Deaths	6	4	4	5
Treatment discontinuations	0	0	9	0
N evaluable for cessation of spread of lesion	98	102	122	130
Cessation of spread of lesion at 2 days (i.e., 48-72 hours)	75/98 (76.5%)	100/102 (98%)	89/122 (73%)	129/130 (99.2%)

Figure A. Meta-Analysis for Cessation of Spread of Lesion at 2 Days



The results of the random effects meta-analysis in patients with erysipelas demonstrate that there is a statistically significant treatment difference for the endpoint of cessation of the spread of cellulitis/erysipelas in favor of sulfonamides compared to UV light. The treatment effect of sulfonamides compared to UV light in cellulitis/erysipelas was estimated to be approximately 24 percent with a lower 95 percent confidence bound of approximately 18 percent based on the meta-analysis of the two studies.

An early on-therapy clinical evaluation as a primary efficacy endpoint in ABSSSI has support from other publications:

Contains Nonbinding Recommendations

- Skin infections of the hand caused by *S. aureus* or *S. pyogenes* that involved underlying tendon-sheaths showed a mean time to resolution of fever at 3.7 days for patients that received penicillin and at 12.0 days for patients that did not receive an antibacterial drug (Florey and Williams 1944)
- A primary endpoint of *days to no advancement of cellulitis* found that approximately 85 percent of all patients in the trial had no advancement of cellulitis at a day 2 time point regardless of whether the patient received the antibacterial drug therapy in a hospital or at home (Corwin, Toop, et al. 2005)
- Before the availability of antibacterial drugs in 1928, 142 patients with erysipelas were treated with nonantibacterial therapies (intramuscular administration of horse serum antitoxin) and 78.1 percent were considered *cured* at day 7 (Symmers 1928), suggesting that an efficacy evaluation for antibacterial drugs much earlier than day 7 is appropriate for the noninferiority trial design in ABSSSI

The treatment difference estimated from the two studies cited above is probably a conservative estimate for the following reasons:

- UV light therapy appeared to result in more favorable outcomes among patients with cellulitis/erysipelas (Lavender and Goldman 1935; Titus 1934; Ude and Platou 1930; Ude 1931; Sutherland and Day 1935)
- Before the availability of antibacterial drug therapy, morbidity (bacteremia) and mortality were observed in patients with skin abscesses caused by *S. aureus* (Skinner and Keefer 1941)
- In comparison to a sulfonamide antibacterial drug, antibacterial drugs available today are probably more effective therapies for ABSSSI (Spellberg, Talbot, et al. 2009)

Summary and Selection of Noninferiority Margin for ABSSSI

The overall data support the treatment difference to be conservatively estimated at 18 percent for antibacterial drugs in the treatment of ABSSSI for the endpoint based on lesion size assessment. Because this appears to be a conservative estimate, further discounting of the treatment effect may not be necessary and thus M_1 is estimated to be 18 percent. These scientific data provide support for the selection of a noninferiority margin of 10 percent that preserves some of M_1 based on an endpoint of lesion size assessment. Sponsors should discuss the selection of a noninferiority margin greater than 10 percent with the FDA in advance of trial initiation.