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Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment Guidance for Industry



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


**June 2020
Clinical/Antimicrobial**





Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment Guidance for Industry

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Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment Guidance for Industry¹

This guidance represents 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 office 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 community-acquired bacterial pneumonia (CABP). Specifically, this guidance addresses the FDA's current thinking about the overall development program and clinical trial designs for drugs to support an indication for the treatment of CABP.²

This guidance does not discuss 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* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.³

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

¹ This guidance has been prepared by the Division of Anti-Infectives 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 regulated by CDER unless otherwise specified.

³ We update guidances periodically. To make sure you have the most recent version of guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

II. BACKGROUND

CABP is defined as an acute bacterial infection of the pulmonary parenchyma associated with chest pain, cough, sputum production, difficulty breathing, chills, rigors, fever, or hypotension and is accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph. Common typical bacterial pathogens that cause CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. Atypical bacterial pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* also cause CABP.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

In addition to the expected nonclinical toxicology/pharmacology studies (see Section III. C. 1, Pharmacokinetic/Pharmacodynamic Considerations), sponsors should provide nonclinical data from in vitro studies and in vivo animal studies demonstrating activity against one or more of the commonly implicated pathogens for CABP.

2. Drug Development Population

The trial population should include individuals who have CABP, as defined in section II, Background.

3. Efficacy Considerations

Noninferiority trials are acceptable to support an indication for the treatment of CABP. A showing of superiority to an effective control would also be acceptable. Historical data show that antibacterial drugs demonstrate a considerable treatment effect compared with nonantibacterial therapies on clinical response evaluated on day 4 of therapy.

The Agency generally expects sponsors to conduct two adequate and well-controlled trials in CABP to establish substantial evidence of effectiveness. Alternatively, a single adequate and well-controlled trial in CABP with confirmatory evidence (e.g., efficacy in another indication or data from a phase 2 clinical trial in CABP) can provide substantial evidence of effectiveness. Sponsors should discuss their proposed development program with the Agency, including the confirmatory evidence that would be used to support the efficacy findings from a single trial.⁴

⁴ See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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4. *Safety Considerations*

If the same or greater dose and treatment duration have been evaluated in other indications, safety data from these indications can be used to support safety for CABP. Sponsors should discuss the appropriate size of the premarketing safety database with the Agency during development.

B. *Specific Efficacy Trial Considerations*

1. *Trial Design*

CABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. See section III. B. 4, Randomization and Blinding, for additional discussion about double-blind trials. Placebo-controlled trials are not appropriate for this indication except when they are add-on superiority trials in which patients receive either a placebo or an investigational drug added to standard-of-care antibacterial drug therapy.

2. *Trial Population*

The trial population for efficacy trials should include patients with CABP based on the entry criteria described in section III. B. 3, Entry Criteria. The FDA recommends that all patients in trials of an intravenously administered drug have a Pneumonia Patient Outcomes Research Team (PORT) classification of III or higher (Fine et al. 1997) and at least 25 percent should have a PORT classification of IV or V. The reasons to exclude patients with a PORT II classification from trials for intravenously administered drugs include the milder severity of illness in general and the fact that patients with a PORT II classification are more likely to be treated appropriately with oral antibacterial drug therapy. For trials in which most patients would be treated as outpatients, all patients should have PORT II or PORT III classifications, with at least 50 percent PORT III. Sponsors should discuss the trial population with the Agency in advance of a phase 3 trial.

3. *Entry Criteria*

a. *Clinical, radiographic, and microbiologic entry criteria*

Sponsors should use radiographic evidence as well as the entry criteria outlined in Table 1 to select patients for enrollment in a CABP trial.

Table 1. Entry Criteria for a CABP Trial

At Least Two Symptoms	At Least Two Vital Sign Abnormalities	At Least One Finding of Other Clinical Signs/Laboratory Abnormalities
<ul style="list-style-type: none">- Difficulty breathing- Cough- Production of purulent sputum- Chest pain	<ul style="list-style-type: none">- Fever- Hypothermia- Hypotension- Tachycardia- Tachypnea	<ul style="list-style-type: none">- Hypoxemia- Clinical evidence of pulmonary consolidation- An elevated total white blood cell count or leukopenia

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An adequate sputum specimen should be processed by a laboratory according to recognized methods for Gram stain, culture, and in vitro antibacterial susceptibility testing.⁵

Use of rapid diagnostic or nonculture tests may help identify a patient for enrollment in a CABP trial (e.g., urinary antigen test for *S. pneumoniae* or *L. pneumophila*; polymerase chain reaction, serology). If the tests being used are not FDA cleared, sponsors should provide sufficient information about the performance characteristics of the tests determined from analytical validation studies.


The clinical trial of an antibacterial drug also may provide an opportunity to develop and evaluate a new diagnostic test. Sponsors interested in using a clinical trial in patients with CABP as a means to also evaluate a diagnostic test are encouraged to discuss this with the Agency.

b. Exclusion criteria

Exclusion criteria should include the following:

- Aspiration pneumonia
- Hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia
- Patients with known bronchial obstruction or a history of postobstructive pneumonia (this criterion does not exclude patients who have chronic obstructive pulmonary disease)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis 

4. Randomization and Blinding

Patients should be randomized to treatment groups at enrollment. All trials should be double-blind unless there is a compelling reason for not blinding treatment allocation. If trials are single-blind or open-label, sponsors should discuss potential biases with the Agency and how these biases will be addressed before initiating the trial. 

⁵ Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute; see also the American Society for Microbiology, 2011, *Manual of Clinical Microbiology*, 10th edition.



5. *Specific Populations*

The trials should include patients of both sexes, patients of all races, and geriatric patients.⁶ Patients with renal or hepatic impairment may be enrolled, provided pharmacokinetics of the drug has been evaluated in these patients and appropriate dosing regimens have been defined.

Sponsors should discuss drug development in the pediatric populations as early as feasible. The Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration Safety and Innovation Act, states that initial plans for conducting 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 FDA and the applicant.⁷

6. *Dose Selection*

To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate the findings from nonclinical toxicology studies; animal models of infection; pharmacokinetics, safety, and tolerability information from phase 1 clinical trials; and safety and efficacy information from phase 2 dose-ranging clinical trials. Trials assessing drug penetration at the site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve concentrations sufficient to exert an antibacterial effect.

For products with both intravenous (IV) and oral formulations, sponsors should collect pharmacokinetic (PK) data in earlier phase studies to select the appropriate oral dose for the IV-to-oral switch.

7. *Choice of Comparators, Prior Antibacterial Drug Use, and Concomitant Therapy*

In general, the active comparator should be considered standard of care for this indication. When evaluating the current standard of care, the FDA considers recommendations by authoritative scientific bodies (e.g., American Thoracic Society, Infectious Diseases Society of America) that reflect current clinical practice based on clinical evidence and other reliable information.

Ideally, patients enrolled in a CABP clinical trial should not have received antibacterial drug therapy for treatment of CABP before enrollment because such therapy could do the following:

⁶ See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers* (February 2012).

⁷ 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 (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* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

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- Obscure true treatment differences between an investigational drug and the control drug, introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority) (Pertel et al. 2008)
- Particularly influence the efficacy findings based on an endpoint early in therapy (day 4)

However, excluding all patients who have received prior antibacterial therapy also may pose problems, including the following:

- Excluding patients with greater disease severity, which may result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; this could bias trial results toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)
- Certain trial sites may not participate because of concerns that trial treatment would not represent standard of care

A pragmatic approach to these concerns is to (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment as their initial 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 (ideally, there would be few such patients, but up to 25 percent of the patient population may be acceptable). This approach would allow patients in the trial to receive prompt antibacterial drug therapy as clinically necessary, consistent with the standard of care. A prespecified analysis of the efficacy results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy would be important to evaluate.

In general, concomitant antibacterial therapy with an antimicrobial spectrum that overlaps with the spectrum of the investigational drug should not be administered during the trial. Sponsors should discuss the additional antibacterial coverage for atypical pathogens with the FDA before initiating the trial.

8. *Efficacy Endpoints*

a. *Primary endpoint*

The primary efficacy endpoint of clinical success should be defined as improvement at day 4 in at least two (with no worsening) of the following symptoms of CABP compared with baseline: chest pain, cough, amount of productive sputum, and difficulty breathing (Talbot et al. 2016). The protocol should specify symptom evaluations on a four-point scale (absent, mild, moderate, severe), defining improvement as at least a one-point improvement from baseline to the assessment at day 4 (e.g., from severe to moderate, from moderate to mild, or from mild to

absent).⁸ The protocol should clearly describe the ascertainment of patients' symptoms as improvement, no change, or worsening based on the four-point scale.

Another efficacy endpoint can be all-cause mortality at 28 days after enrollment, but feasibility would be an issue in clinical trials in certain patient populations with a greater severity of CABP. Sponsors considering using all-cause mortality as the primary efficacy endpoint should discuss the trial design with the Agency.

b. Secondary endpoints

Following are some examples of secondary endpoints that could be evaluated:

- Improvement at day 4 in at least two (with no worsening) of the following symptoms of CABP compared with baseline: chest pain, cough, amount of productive sputum, and difficulty breathing; *and* improvement in vital signs (i.e., body temperature, blood pressure, heart rate, and respiratory rate)⁹
- Clinical outcome (i.e., improvement/resolution of symptoms of CABP) at the end of therapy)
- Clinical outcome (i.e., resolution of symptoms of CABP) at a fixed time point after randomization and completion of therapy)

c. Intravenous and oral formulations

For drugs available only as an IV formulation, sponsors should conduct trials with the IV formulation alone for the entire duration of therapy, if feasible, or at least until the day 4 assessment is complete. This will allow for the assessment of both the efficacy and the safety of the investigational drug before switching to an oral antibacterial drug. Ideally, the duration of oral antibacterial drug therapy (i.e., days of IV therapy plus days of oral drug therapy) should be as short as possible so sponsors can assess the contribution of the IV investigational drug to overall efficacy after completion of treatment. The criteria for switching to oral antibacterial drug therapy should be included in the protocol.

For drugs that have both an IV and an oral formulation, the protocol should specify the criteria that allow for IV-to-oral switch.

⁸ The Appendix describes the historical treatment benefit of antibacterial therapy at 3 to 5 days following initiation of antibacterial drug therapy. Day 4 was selected as the recommended timing of the primary efficacy endpoint to allow for clinical protocols to provide a window period for assessing the primary efficacy endpoint (i.e., a 24-hour window before and after day 4). Sponsors should discuss with the Agency if a day 3 or a day 5 time point is being considered for the timing of the primary efficacy endpoint in the protocol. See also Toerner et al. 2012. For information about the development of patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

⁹ Improvement or stabilization of vital signs and other signs attributable to CABP should be defined in the protocol. For example, see table 10 in Mandell et al. 2007.

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9. *Trial Procedures and Timing of Assessments*

a. *Entry visit*

Sponsors should collect baseline demographic and clinical information at the entry visit, in addition to microbiologic specimens and laboratory tests, as appropriate.

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

The protocol should specify the evaluation of patients on therapy and at the end of therapy. These visits should capture patient symptoms, physical examination findings, assessments and resolution of adverse effects, if any, and appropriate laboratory tests.

c. *After therapy visit*

The protocol should specify the evaluation of patients 5 to 10 days after completion of treatment. These visits, used to evaluate secondary endpoints, should capture patient symptoms, physical examination findings, assessments and resolution of adverse effects, if any, and appropriate laboratory tests. The trial should assess all-cause mortality at day 28.

10. *Statistical Considerations*

In general, sponsors should submit a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation.

a. *Analysis populations*

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

- **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-ITT (micro-ITT) population** — All randomized patients who have a baseline bacterial pathogen that is known to cause CABP and that is susceptible to the investigational drug and the active control, from an appropriate sputum specimen or blood.
- **Clinically evaluable or per-protocol populations** — Patients who meet the definition for the ITT population and who complete the trial as specified in the protocol.
- **Microbiologically evaluable populations** — Patients who meet the definition for the micro-ITT population and who complete the trial as specified in the protocol.

Sponsors should discuss with the Agency the prespecified primary analysis population before initiating the trial. In general, it is acceptable to consider the ITT population as the primary

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analysis population. For antibacterial drugs with a narrow spectrum of activity (e.g., a drug active against a single genus and species of bacteria), the micro-ITT population will be considered the primary analysis population.

b. Noninferiority margins

Historical experience indicates that there is a relatively large treatment effect of antibacterial drug therapy on clinical response at day 4 (see the Appendix). In general, the selection of a noninferiority margin of 12.5 percent is reasonable for CABP clinical trials using a clinical response endpoint at day 4. In certain circumstances, sponsors may consider a noninferiority margin greater than 12.5 percent. Sponsors should discuss with the Agency a clinically appropriate noninferiority margin before initiating the trial.

c. Sample size considerations

A general framework is provided for sponsors to begin to discuss sample size considerations with the Agency during protocol development. In this illustrative sample size calculation, approximately 225 patients per group is estimated based on the following assumptions: (1) a rate of clinical success for the active control and test therapy of 80 percent, (2) two-sided type I error (α) of 0.05, (3) type II error (β) of 0.10 (power 0.90), (4) a noninferiority margin of 12.5 percent (see the Appendix), and (5) an ITT analysis population.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Evaluation

Sponsors should evaluate the PK/pharmacodynamic (PD) characteristics of the drug using in vitro methods and animal models of infection. Sponsors should also consider the limitations of such models before evaluating the antibacterial drug (Tessier et al. 2002; Gavalda et al. 1997; Legget 1999; Miyazaki et al. 1997; Silverman et al. 2005).

Integration of these PK/PD characteristics of the drug with the findings from phase 1 clinical trials can assist identification of appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials.¹⁰

Sponsors should obtain blood samples from patients in phase 2 and phase 3 clinical trials (sparse sampling) to estimate drug exposure in each patient. Sponsors should perform an exposure-response analysis for clinical outcomes, microbiologic outcomes, and clinically relevant adverse events. If phase 3 trials include a previously unstudied specific population, such as patients with renal or hepatic impairment, collecting plasma drug concentrations from those specific populations can aid in determining necessary dose adjustments.

¹⁰ See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003) and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* (November 1994).

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2.

Labeling Considerations

Generally, the labeled indication should be the treatment of CABP caused by the specific bacteria identified in the clinical trials.



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APPENDIX:

NONINFERIORITY MARGIN JUSTIFICATION FOR CABP

Background

Selecting a noninferiority margin depends on a reliable estimate of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M_1), usually based upon placebo-controlled trials, that can be assumed to hold for the noninferiority trial. After M_1 is established, clinical judgment determines how much of the estimated treatment effect (M_1) should be preserved in determining a clinically acceptable noninferiority margin, referred to as M_2 .

Historical studies and clinical trials of antibacterial drug therapy for bacterial pneumonia provide evidence that antibacterial drugs have the following treatment effects:

- Achieving a greater proportion of patients with favorable clinical responses at time points earlier in the course of antibacterial drug therapy (i.e., at day 3 to day 5)
- Reducing mortality in patients with pneumococcal or lobar pneumonia

An area of uncertainty in evaluating historical data is the spectrum of bacterial pathogens that cause community-acquired bacterial pneumonia (CABP) today. In most of the historical studies and historical controlled clinical trials, CABP was considered synonymous with pneumococcal pneumonia because *Streptococcus pneumoniae* was regularly identified. A review of recently conducted trials showed that less than 20 percent of the total patient populations had documented *S. pneumoniae* (Higgins et al. 2008). CABP is also caused by other pathogens such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*, as well as atypical bacteria such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. Limited information is available on a treatment effect of antibacterial drugs in CABP caused by *M. pneumoniae* (Kingston et al. 1961). A fundamental assumption is that historical response rates in infections such as *S. pneumoniae* CABP are relevant to response rates in modern infections with sensitive organisms.

The steps taken to determine a noninferiority margin for the primary outcome measure based on the outcome assessments of chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing at day 4 after enrollment is as follows:

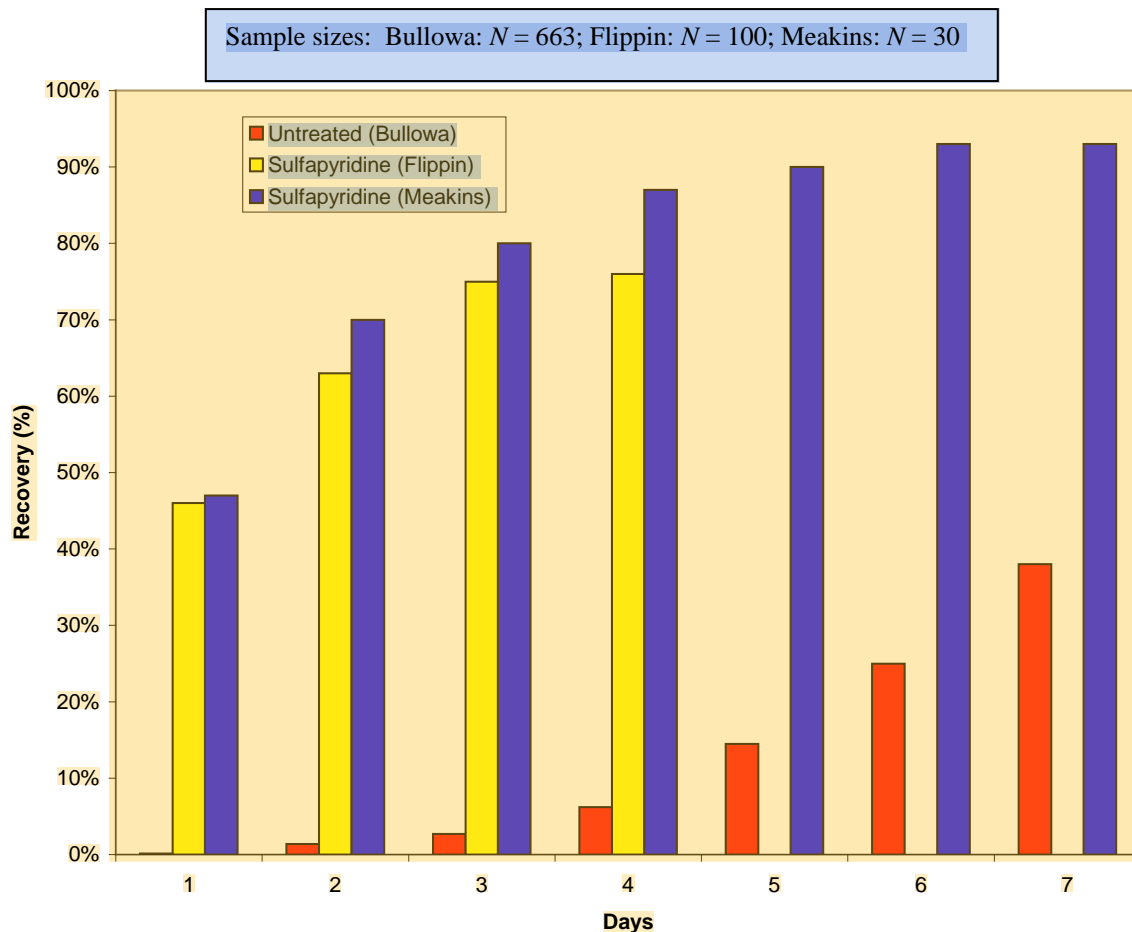
Primary Endpoint Based on Clinical Outcome Assessments at Day 4 after Enrollment

Studies conducted around the time of the introduction of antibacterial drug therapy described clinical responses among untreated patients and patients treated with antibacterial drugs. These observational studies provide an estimate of the effect of antibacterial drugs on clinical response endpoints other than mortality.

Several papers described the clinical course of patients with pneumococcal pneumonia in a similar way; patients were recorded as having a successful clinical result by demonstrating fever

resolution and accompanying improvement and resolution of other signs and symptoms of pneumonia. For example, a description in one of the papers stated, “This fall in temperature was in all cases accompanied by a conspicuous reduction in the pulse and respiratory rates, and the patients were improved subjectively” (Meakins and Hanson 1939). One study described the clinical course of 663 patients who did not receive antibacterial drug therapy (Bullowa 1937), whereas two other studies included patients who received antibacterial drug therapy. One study described the clinical course over the first 4 days after therapy in 100 patients with pneumococcal pneumonia (Flippin et al. 1939) and another study described the clinical course over 7 days in 30 patients with pneumococcal pneumonia (Meakins and Hanson 1939). Figure 1 compares the three studies in the rates of clinical recovery, defined generally as the improvement in both clinical signs and symptoms.

Figure 1. Rates of Clinical Recovery Recorded at Each Day (Meakins and Hanson 1939; Bullowa 1937; Flippin et al. 1939)

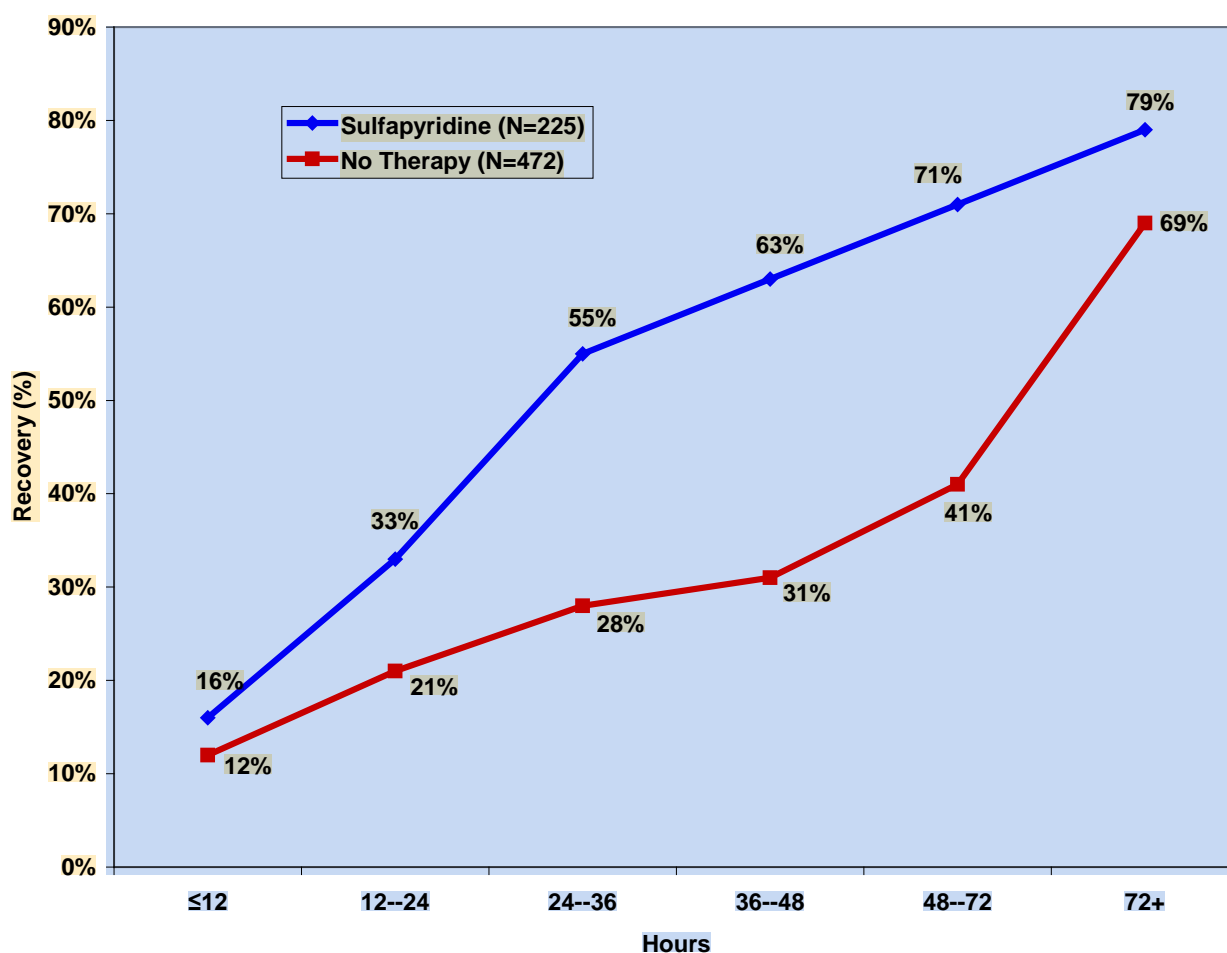


The difference in clinical recovery rates at day 4 between patients in the two treatment studies and patients in the study without treatment were 72 percent and 77 percent.

Figure 2 shows the rates of clinical recovery in an observational study of patients with pneumococcal pneumonia who received antibacterial drug therapy (sulfapyridine) and a group of

patients who received no specific therapy. Clinical recovery was defined as a “permanent drop in oral temperature below 100°F, with subsidence of other symptoms of acute infection” (Finland et al. 1940). Time points at 36 to 48 hours and 48 to 72 hours after therapy initiation show the greatest treatment effect on clinical recovery. The treatment difference is approximately 30 percent (95 percent confidence interval: 22 percent, 37 percent) at the 48- to 72-hour time point. Clinical observations that were reported at any time after the 48- to 72-hour assessment are displayed as 72+ in Figure 2. The time points after 72 hours (i.e., 72+) included recovery time points out to several weeks following therapy completion.

Figure 2. Rates of Clinical Recovery of Acute Bacterial Pneumonia (Finland et al. 1940)



Another paper described the outcomes among pediatric patients with pneumococcal pneumonia and provides additional support for a treatment effect of antibacterial drugs relatively early in therapy. The mean time to clinical recovery was 4.7 days among patients who received antibacterial drug therapy whereas patients who did not receive antibacterial drug therapy had a mean time to clinical recovery of 8.9 days (Wilson et al. 1939).

The clinical response endpoints that were evaluated in each of these studies were not well defined. The studies evaluated both signs and symptoms together. A large treatment effect was observed at the early time point in the course of therapy (i.e., day 3 to day 5 after therapy

initiation) for an endpoint that included improvement in both signs and symptoms. The studies show that the treatment differences become smaller at times beyond day 3 to day 5 of therapy. Features of these studies that support their use as an estimate of M_1 at day 4 include the following:

- The studies documented bacterial pneumonia, all as *S. pneumoniae*.
- The estimate of the treatment difference appears to be large and is consistent across studies.
- Some patients included in the *no therapy* group in Figure 2 were patients who had signs and symptoms of milder pneumonia. Even after the availability of antibacterial drugs, the clinician chose not to treat such patients with antibacterial drug therapy because of the likelihood of spontaneous recovery. Including patients more likely to experience spontaneous recovery of pneumonia in the no-therapy group led to an underestimate of the true treatment difference among patients with more serious disease.
- The clinical response measurements are plausible consequences of treating an infection.

The limitations of these studies include the following:

- The studies were not randomized
- Historically controlled studies created a greater level of uncertainty in estimating treatment differences
- The clinical response evaluations were not defined
- The clinical response evaluations included improvement in both signs and symptoms together and did not separately evaluate improvement in chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing

The treatment difference appears to be large for an endpoint based on clinical outcome assessments earlier in the course of therapy for CABP. However, the results are variable, ranging from the point estimate of 30 percent treatment difference at a 48- to 72-hour time point noted in Figure 2 to a point estimate of 77 percent treatment difference at day 3 noted in Figure 1.

It is difficult to provide a precise numerical value for the treatment effect of a proposed primary endpoint of symptom improvement at day 3 to day 5. However, an M_1 of at least 20 percent appears to be a reasonably appropriate and conservative estimate, accounting for the uncertainties with clinical recovery in the historical literature. A conservative estimate of M_1 at 20 percent is still large enough to support selecting a noninferiority margin (M_2) of 12.5 percent for the endpoint of symptom improvement at day 4. Selecting the noninferiority margin (M_2) is a matter of clinical judgment and should be justified by the sponsor.

Contains Nonbinding Recommendations

209 The Agency also evaluated the literature from just before and just after the introduction of
210 antibacterial drug therapy in the mid-twentieth century (Finland 1943; Dowling and Lepper
211 1951; Austrian and Gold 1964). The Agency found support for a treatment effect of antibacterial
212 drug therapy on the endpoint of all-cause mortality.

213 214 **Summary**

215
216 The available data provide a basis for a noninferiority margin specification for primary efficacy
217 outcome assessments based on symptom improvement at day 4 compared with baseline.