Guidance for Industry

Acute Bacterial Sinusitis: Developing Drugs for Treatment

DRAFT GUIDANCE

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For questions regarding this draft document contact Steven Gitterman at 301-796-1600.

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

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Clinical Antimicrobial
Revision 1

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 sinusitis (ABS). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and designs of clinical trials for drug products to support an indication for treatment of ABS.[2] It is the intention of this guidance to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products and pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address the development of drugs for other purposes such as prevention of ABS or treatment of chronic sinusitis, or developing drugs for the nonantimicrobial treatment of sinusitis. As the science of the treatment of ABS evolves, this guidance may be revised as new information accumulates.[4]

This guidance revises the draft guidance for industry *Acute Bacterial Sinusitis — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of

[1] This guidance has been prepared by the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidance documents, sponsors are encouraged to contact the divisions to discuss specific issues that arise during the development of antimicrobial drug products.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

ABS. It also supersedes, with regard to the development of drugs to treat ABS, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective drugs (Systemic*) and *Clinical Development and Labeling of Anti-Infective Drug Products*, as well as the joint FDA/Infectious Disease Society of America's *Guidelines for the Evaluation of Anti-Infective Drug Products*).

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of the treatment of ABS.

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

There have been a number of public discussions regarding the design of clinical trials to study ABS since the FDA last published draft guidance on the development of antimicrobial drugs for the treatment of ABS in 1998. These discussions have focused primarily on the appropriateness of noninferiority trial designs for ABS and other important study design issues such as the following:[5]

- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes

Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below.

[5] In October 2003, the Anti-Infective Drugs Advisory Committee (AIDAC) discussed ABS clinical trials with a focus on the use of noninferiority designs (see http://www.fda.gov/ohrms/dockets/ac/cder03.html#Anti-Infective). In September 2006, the AIDAC addressed appropriate use of noninferiority studies for ABS in the context of a specific product (see http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective). More recently, in a December 2006 joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee, the issue of noninferiority study design was discussed in the context of evaluating the risk-benefit profile of a drug. In this case, ABS, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia were the indications under discussion (see http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective).

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New drugs being studied for ABS should have preclinical data documenting activity against the most commonly implicated pathogens associated with ABS (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*). Animal models of ABS have been developed in both rabbits and mice, particularly for *S. pneumoniae* infection, and pathological and histological responses to antibacterial treatment have been shown in both species. Although these models may contribute to demonstrating proof of concept in the treatment of ABS (or for comparing in vivo activity of different antimicrobials), the results should be carefully interpreted when being used to help design subsequent human studies. Animal studies should not be considered a substitute for the clinical trials in patients with ABS that should be conducted to evaluate safety and efficacy of the drug. However, animal models may be especially valuable for evaluating antimicrobial activity against antibiotic resistant organisms or specific microbial serotypes that occur less commonly in clinical studies.

It is important to understand the pharmacokinetics, metabolism, and distribution of the test drug in the animal being studied to be able to use the data from the animal model to inform the design of studies in other animal models or subsequent clinical studies (e.g., data from animal studies can be one of the components considered in selection of doses that will be evaluated in subsequent clinical studies). Animal models of other respiratory tract diseases (e.g., an animal model of pneumonia) also can provide relevant information on the antimicrobial activity of the test drug for the pathogens that are associated with ABS.

2. Drug Development Population

Previously, the FDA's clinical definition of acute sinusitis was "infection of one or more of the paranasal sinuses." To better identify those patients most likely to benefit from antimicrobial therapy, this guidance defines ABS as "inflammation of the paranasal sinuses as a result of *the presence of a bacterial pathogen within the sinus space* when the duration of illness is less than 4 weeks." In addition, this guidance considers ABS to be restricted to maxillary disease with or without involvement of other sinuses, the most common presentation of acute bacterial sinusitis. Although isolated disease of the frontal or sphenoid sinus exist as clinical entities, they are rare and have a different pathophysiology, microbiology, and clinical course from maxillary sinusitis.[6]

Although the medical literature commonly refers to disease of the sinuses in conjunction with nasal symptoms as *acute rhinosinusitis*, the FDA considers rhinitis and sinusitis as distinct disease entities. The administration of antimicrobials is appropriate only for study of bacterial

[6] The consideration in this guidance of trial subjects being restricted to patients with maxillary sinusitis is primarily because of pragmatic concerns in ABS clinical trial designs. The inclusion of patients with nonmaxillary sinusitis in a clinical superiority study may be acceptable as part of a phase 3 study depending on the overall drug development program.

infection of the sinuses. Rhinitis symptoms without sinus disease are most commonly caused by viral infection, allergic rhinitis, and/or vasomotor instability. Since the FDA has approved nonantimicrobial drugs specifically for rhinitis symptoms alone, it is important to separate the effect of antimicrobial therapy on acute bacterial sinusitis from treatment of nasal symptoms caused by nonbacterial sources.

3. Efficacy Considerations

FDA review of previous ABS studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABS by antimicrobials (a precondition for a noninferiority trial). Accordingly, only superiority trials are currently recommended for ABS studies.

The goal of ABS clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABS caused by *H. influenzae*, *S. pneumoniae*, or *M. catarrhalis*. Some studies have also implicated *Staphylococcus aureus* as a pathogen in ABS in the setting where this has been the sole pathogen isolated. If sponsors wish to add additional organisms to this indication, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in ABS.

The number of studies needed for approval of an ABS indication depends on the overall development plan for the drug product under consideration. If the development plan for a drug product has ABS as the sole marketed indication, then at least two adequate and well-controlled trials establishing safety and efficacy should be conducted for this indication.

When two studies are conducted for an ABS indication, we strongly recommend that at least one study be conducted with sinus puncture and aspiration from all patients (see section III.B.2., Study Population, and section III.B.3., Study Inclusion Criteria). A design with microbiological information on all patients offers the strongest likelihood of success by ensuring that all patients in the primary analysis population have a documented bacterial infection and that an adequate number of patients with each of the common bacterial pathogens has been enrolled (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*). Microbiological confirmation also permits analysis of treatment response by individual pathogen. Although sinus puncture with aspiration is recommended for the second study as well, endoscopy or clinical criteria alone can be sufficient for defining the primary analysis population in a second superiority study.

A single study for an ABS indication may be appropriate if there are data from other clinical studies demonstrating effectiveness in other respiratory tract diseases and there is additional supportive information such as pharmacokinetic and pharmacodynamic studies demonstrating concentration of the antibacterial drug in the sinuses at a level expected to be active against the common pathogens causing ABS. For example, evidence of efficacy from community-acquired pneumonia (CAP) trials may be supportive of a single superiority trial of ABS because of the similar microbiology and greater seriousness of CAP relative to ABS. If one study is conducted, sinus aspiration for all study patients should be performed to analyze outcome by specific infecting pathogen.

Currently, there are no surrogate markers accepted by the FDA as substituting for clinical outcomes in ABS studies. Sponsors who wish to propose a surrogate marker for clinical outcome or the initial diagnosis of ABS should discuss this with the FDA early in the drug development process.

4. Safety Considerations

Antimicrobials with clinically significant toxicity should not be considered appropriate for study of this indication unless treatment of a more seriously ill patient population is being considered.

A sufficient number of patients should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety. This information can be derived from studies of the new drug for infections other than ABS if exposure is similar to or greater than the exposure for ABS; however, if ABS is the sole indication being studied by a sponsor, it is likely that additional patients may need to be studied for safety beyond the number of patients needed to show clinical efficacy for ABS. The total number of patients needed for a drug development program that includes an ABS indication should be discussed with the FDA early in the drug development process.

B. Specific Efficacy Trial Considerations

1. Study Design

Currently, we recommend only superiority trials for ABS studies. Sponsors who are considering a noninferiority trial for ABS should justify a proposed noninferiority margin to the FDA as early as possible during protocol development and before study initiation. This situation is discussed further in section III.B.11., Statistical Considerations.

Superiority studies in the treatment of ABS can consist of the following general forms:

- **Placebo-controlled study with a background of *optimized* nonantimicrobial therapy** — This design tests the safety and efficacy of an antimicrobial as an addition to a standardized regimen of analgesic and decongestant medications compared to the same standardized regimen plus placebo.

- **Delayed versus immediate therapy** — Patients in both study arms receive an *active* therapy, but administration of the comparator treatment is delayed relative to the experimental drug. To demonstrate efficacy, the experimental arm (immediate therapy) should demonstrate superiority over the comparator arm (delayed therapy) using an approach such as time to resolution or by evaluating response at a predetermined fixed time point when differences in response between the two groups are expected.

- **Dose-response** — Patients in each study arm receive different antimicrobial doses (or dosing regimens) together with standardized nonantimicrobial therapy. To demonstrate efficacy, the arm receiving a higher dose (or more intensive therapy) should be superior to the lower dose (or less intensive) regimen.

- **Superiority of the study antimicrobial to another antimicrobial** — Patients in one arm receiving the test drug (with standardized background nonantimicrobial therapy) are compared to patients in a control arm receiving another antimicrobial drug (with standardized background nonantimicrobial therapy). To demonstrate efficacy, the arm receiving the test antimicrobial should demonstrate superiority to the arm receiving the control antimicrobial.

A three-arm study with the experimental treatment group, an active-controlled arm (e.g., an antibacterial agent approved for ABS), and a placebo-controlled group permits the demonstration of superiority and also can provide risk-benefit information relative to an approved comparator.

ABS trials should be parallel group designs as crossover designs may be subject to carry-over and period effects.

Study designs should provide appropriate provisions for patient safety. Review of previous placebo-controlled studies of ABS have not shown a risk to placebo-treated recipients that make future placebo-controlled trials unethical; the risk from placebo treatment may be similar to that associated with antibacterial therapy since low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. The occurrence of common but less-severe adverse events (e.g., diarrhea) from antibacterial drugs also can be relevant in assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment effect may be small. *Rescue* therapy can be incorporated into the study design so that individual patients are treated at the time a *failure* outcome is assigned; this addition may serve to mitigate concerns regarding inclusion of a placebo arm in an ABS trial.

At the present time, the FDA does not recognize different forms of ABS based on disease severity at presentation. However, we recognize that investigators may be less likely to enroll patients presenting with *severe* disease in a placebo-controlled trial than patients with milder symptoms, and that enrollment of hospitalized patients may be incompatible with a placebo-controlled study. We also recognize that treatment of severe disease is where an antimicrobial treatment effect may be greatest. If sponsors wish to study patients with severe disease (or hospitalized patients), we strongly encourage discussion with the appropriate review division regarding protocol design.

2. Study Population

ABS clinical trials can enroll male and female patients 12 years old and older, if appropriate.[7]

[7] Pediatric patients 6 months and older can be included in adult ABS studies if a dose, regimen, and formulation for these patients has been identified that yields drug exposure similar to that in adults; pediatric patients over 12 years of age often receive the same dose and formulation as adults and usually can be enrolled in these studies. However, sinus puncture may not be appropriate for pediatric patients in certain situations. Sponsors should discuss with the FDA studies where sinus puncture in pediatric patients is planned before initiation of the trial to ensure compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations. Other considerations for compliance with Subpart D include whether there are sufficient safety data to allow study of pediatric patients, and the acceptability of both the trial design and diagnostic procedures in pediatric patients. Sponsors pursuing an indication for ABS are strongly encouraged to discuss the requirements for pediatric studies in their overall drug development program with the FDA early in development.

ABS should be diagnosed by a combination of signs and symptoms with radiographic imaging included with the initial assessment to increase diagnostic specificity for bacterial disease. Documenting the presence of bacteria in the sinus cavity by sinus aspiration can be a potentially important means to enrich the study population for analysis and can also serve to confirm that enrollment procedures have succeeded in entering an adequate percentage of patients with bacterial disease.

To improve specificity for ABS (i.e., to better select for bacterial rather than viral sinusitis), patients should have symptoms for a minimum of 7 to 10 days before enrollment, without improvement over the 3 days immediately before enrollment.

An alternative study design can be used where patients are enrolled at days 4 to 7 and a 3-day run-in period is used before randomization. Randomization of patients with symptoms that have not improved over the 3-day run-in period may enrich the study population for patients with a bacterial etiology of sinusitis.

3. Study Inclusion Criteria

a. Symptoms

Symptoms that can be present in patients with ABS include the following:

- Maxillary tooth pain (unilateral findings can be more specific)
- Facial pain (unilateral findings can be more specific)
- Headache
- Purulent nasal discharge (unilateral findings can be more specific)
- Fetor oris (bad breath)
- Cough
- Nasal obstruction

b. Signs

Signs that can be present in patients with ABS include the following:

- Purulent secretions from sinus ostia on examination
- Abnormal sinus transillumination
- Pain on palpation over sinuses
- Facial swelling

c. Generalized signs and symptoms

Additional generalized signs and symptoms that are consistent with a diagnosis of ABS but are otherwise nonspecific include:

- Fever (temperature greater than 38.5 degrees Centigrade)
- Malaise

All signs and symptoms present at baseline (and during time on study) should be recorded. The minimum subset of specific signs and symptoms needed for enrollment should be defined in the study protocol as part of the inclusion criteria for the study.

Although review of the medical literature has not identified a combination of patient characteristics with high specificity for bacterial sinusitis relative to other causes of acute sinusitis, the presence of a greater number of symptoms is associated with a higher likelihood of bacteria being isolated by sinus aspiration. A duration of illness greater than 7 to 10 days at the time of presentation and a history of previous episodes of acute sinusitis also improve specificity for bacterial disease.

Radiographic findings consistent with acute sinusitis also should be documented to be present at baseline (see section III.B.5.a., Radiography).

4. Exclusion Criteria

The following patients should be excluded from ABS trials:

- Patients with symptoms attributed to sinus disease for longer than 4 weeks.
- Patients with disease history consistent with allergic and other types of rhinitis.
- Patients with isolated frontal and sphenoidal disease given the different pathophysiology and etiologic pathogens. Patients with maxillary plus other sinus disease can be included.
- Patients with cystic fibrosis.
- Immunocompromised patients or patients with other medical conditions that may affect interpretation of the effect of study medications.
- Patients who are allergic to any of the study medications.
- Patients with nasal polyposis.

Sponsors can exclude patients who have received antimicrobial therapy for the current episode of ABS, even if baseline aspiration yields a treatable pathogen. If patients who have received prior antimicrobial therapy are included, they should be stratified before enrollment to ensure balance across the treatment arms.

5. Additional Study Entry Procedures

a. Radiography

Previous studies have attempted to identify radiographic abnormalities associated with bacterial causes of sinusitis versus other etiologies. In general, these modalities, including plain sinus radiography, computed tomography, magnetic resonance imaging, and ultrasound, have been nonspecific for the presence of bacteria by sinus puncture. However, radiography may have a strong negative predictive value for bacterial sinusitis (i.e., the absence of radiographic abnormalities identifies patients with a lower likelihood of a bacterial sinus infection). Because of this, radiological assessment is strongly recommended as a means to enrich the study population. In clinical studies, the number of patients who are screened for enrollment but then

have negative radiography should be recorded and included in the study report. The clinical characteristics of patients screened but not enrolled also should be recorded.

b. Baseline sinus aspiration and endoscopy

The microbiological diagnosis of ABS is based on isolating a bacterial pathogen from a specimen obtained by maxillary sinus puncture at baseline. Gram stain of the aspirate material with examination for white blood cells (WBCs) also should be performed, as well as antimicrobial susceptibility testing of bacterial isolates.

A clinical development program for the treatment of ABS should provide adequate microbiological information to evaluate the in vivo activity of the experimental drug for treating pathogens associated with ABS. As noted earlier, a clinical development plan where at least one trial includes sinus aspiration on all patients should be conducted to obtain the microbiological data to support an indication of ABS.

Endoscopy can be used to enrich the patient population in a second clinical trial; however, at this time, we do not consider endoscopic cultures to be sufficiently reliable to substitute for sinus puncture samples when obtaining the microbiological data to support inclusion of organisms in an ABS indication (see section III.A.3., Efficacy Considerations).

Other techniques, such as the placement of a small-bore indwelling catheter during treatment, can be useful for examining the microbiological response to treatment across treatment arms over time in phase 2 studies.

When sinus puncture and aspiration or endoscopy is performed on all patients as part of the clinical study design, the primary patient population for analysis should be patients with positive bacterial culture at enrollment. If baseline sinus puncture or endoscopy of all patients is not included as part of a specific protocol, it is strongly recommended that a subset of patients have microbiological samples obtained via sinus puncture or endoscopy across all sites to ensure that the *a priori* estimate of bacterial disease is correct. An unexpectedly high enrollment of patients with sinusitis from a nonbacterial etiology will likely lead to a study population that will not respond to antibacterial therapy.

When microbiological sampling is performed, investigators should be blinded to the microbiological data obtained at entry. This approach can be used to eliminate possible bias in evaluating the relationship between in vitro resistance at baseline and clinical outcome. In vitro resistance (or infecting pathogen) at entry should not be used to alter treatment assignment or study conduct; as discussed below, rescue treatment can be provided to all patients regardless of microbiological status at entry if the study criteria for clinical failure are met while on the originally assigned treatment.

The protocol should describe the specific methods to be used for obtaining, transporting, and processing specimens when aspiration or endoscopy is performed. The specific culture techniques to be used on specimens also should be described.

6. Randomization, Stratification, and Blinding

Patients should be randomized for receipt of study drugs at enrollment. All studies should be double-blinded for study therapy and assessment of outcome unless there is a clearly compelling reason why this cannot be done.

7. Dose Selection

Data from phase 2 dose-ranging studies can be integral to selecting an appropriate dose for phase 3 clinical trials. Additional information from phase 1 and phase 2 pharmacokinetic and pharmacodynamic studies (including information regarding sinus penetration of the drug) also can be valuable.

8. Concomitant Medications

ABS clinical trials should determine the additional contribution of the antimicrobial drug to clinical outcome beyond nonantimicrobial therapies. Lack of standardization of concomitant medications can introduce an important source of confounding in clinical trials if there are imbalances in receipt of nonantimicrobials between trial groups. Such confounding may occur even if the number of patients receiving concomitant medications is similar between study groups but the reasons for administering concomitant medications differ. Confounding also may occur when the patients in one group who receive concomitant medications differ in baseline characteristics from those patients who do not receive concomitant medications. Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications. This can be accomplished through a protocol-specified nonantimicrobial background regimen with the dose and frequency of use similar for all patients in the trial; however, the use of standardized, nonantimicrobial therapy in the protocol should be based on experimental evidence that the treatment is effective. At a minimum, the protocol should specify appropriate options for nonantimicrobial therapies during the study.

Assessment of the need for concomitant medications as an endpoint may not be an accurate surrogate for persistent patient symptoms unless the presence of such symptoms is confirmed by a patient- or caregiver-reported outcome tool that shows continued symptoms at the time of administration of the concomitant medication. Effort should be made to capture all concomitant medication use on a patient- or caregiver-reported tool and to relate this information to patient symptoms.

9. Efficacy Endpoints

a. Evaluation of clinical response

The primary emphasis of the study should be the effect of the antimicrobial drug on outcomes that are clinically important to patients. Assessment of clinical response at each time point should not be limited solely to symptoms identified at the time of enrollment. For example, if a patient is enrolled with ABS in one sinus and develops ABS in the contralateral sinus during therapy while symptoms referable to the first sinus are still improving, that patient should not be

considered a clinical success. Patient outcome should be based on response per patient rather than per sinus (i.e., outcome is measured identically regardless of whether unilateral or bilateral disease is present).

If improvement or resolution of symptoms is the primary outcome measure of a study, then assessment over time on this measure should be the primary efficacy analysis. An alternative would be to use response at a fixed time point as the primary study endpoint. However, a fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-resolution analysis. For example, clinical outcome at greater than 2 weeks after onset of therapy may not show a difference between treatment arms since most patients will be clinically cured by this time regardless of the administration of antimicrobials. Sponsors who choose to use response at a fixed time point as the primary outcome (i.e., as the *test-of-cure* assessment) should provide evidence to support the selection of that specific time point. Measuring clinical response in an ABS trial can be approached in two ways: as a categorical response (i.e., success or failure based on complete resolution of symptoms) or as a composite outcome scale score.

1. Primary clinical outcome based on complete resolution of symptoms

- *Clinical success.* Clinical success can be documented when a patient exhibits complete resolution of clinically meaningful symptoms present at enrollment and the absence of new symptoms or complications attributable to sinusitis.

- *Clinical failure.* Clinical failure can be documented as follows:

  – Development of complications of ABS such as meningitis and/or brain abscess, subdural empyema, cortical or sinus vein thrombosis, or extension of disease to the orbit of the eye.

  – Protocol defined worsening of symptoms or failure to improve at certain time points (e.g., 72 hours after treatment onset).

  – Treatment with nonstudy antibacterial agents for ABS or a related condition.

  – Lack of complete resolution of symptoms at the study-defined early follow-up visit.

We recommend that the primary efficacy endpoint be time to clinical success, defined as above for the period from the start of study drug to complete relief of symptoms. Use of an appropriate patient-reported outcome (PRO) tool for the evaluation of acute symptoms is preferred.[8] The method of assessment should be a well-defined and reliable method of

[8] The use of a validated patient-reported outcome (PRO) instrument, even for a categorical response, can yield greater assurance that symptoms are being measured identically across patients. For more information regarding the development of PRO measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

assessing patient response. Patients designated as a clinical failure at any time point should be designated as clinical failures for all subsequent follow-up visits.

2. Primary clinical outcome based on a scale

If a PRO instrument is used for measuring responses that will be based on a scale score, then the score rather than an endpoint of complete symptom resolution should be used as the outcome variable. Use of a scale score permits interpretation of partial responses short of complete symptom resolution (i.e., *improvement*).

The amount of improvement determined to be clinically meaningful (and, therefore, appropriate for regulatory decisions) should be determined during instrument development and discussed with the FDA before study initiation. Statistically significant differences between comparator regimens can be insufficient for demonstrating benefit if the differences have not been shown to be clinically meaningful (i.e., above the minimum important difference). As an example, signs or symptoms used to diagnose ABS that may be important to a clinician, such as the color of nasal secretions, may not be an important outcome to patients and, therefore, may be weighted lower as part of the response instrument scale score.

An outcome scale can be used for describing categorical responses (e.g., *success*, *improvement*, and *failure*) at each time point if the criteria for the categories have been well-developed and validated.[9]

b. Clinical relapse or recurrence

Patients who experience clinical improvement without complete resolution of symptoms but then worsen should be considered clinical failures (i.e., there should be no separate category for relapse). Patients who experience complete resolution of symptoms of ABS for at least 48 hours and then experience further symptoms indicative of ABS before the early or late follow-up visit should be considered clinical recurrences for that follow-up visit.

Clinical recurrence can be evaluated as a secondary endpoint. Sinus puncture in patients who experience further symptoms (recurrence) may be valuable, as this would allow a differentiation between patients who may still harbor the initial pathogen compared to those patients who have acquired a new pathogen or have a noninfectious etiology for symptoms. Bacterial isolates obtained from clinical recurrences should be subjected to an appropriate in vitro method (e.g., pulse field electrophoresis gel) to determine if the original isolate and the isolate obtained from the recurrence episode are indistinguishable.

[9] If a PRO instrument is used for assessing the primary study endpoint, then it may be possible to use time to reach a specific criterion of clinical improvement as the primary efficacy outcome (i.e., before complete resolution of symptoms). However, use of such a measure as the primary efficacy analysis should be discussed with the FDA before study initiation.

c. Adverse events or receipt of additional antibacterial therapy

Patients who discontinue therapy because of an adverse event should be evaluated at the time of discontinuation of the study medication. These patients should not be considered *withdrawn from the study* in terms of overall evaluation; investigators should continue to follow all such patients at study visits as scheduled and continue to record information on both safety and efficacy outcomes. If at the time study medication is discontinued the patient is alive, without complications, and does not receive additional antimicrobial therapy, then the patient should be evaluated following the protocol criteria; discontinuation of therapy because of an adverse event should not automatically be considered a clinical failure.

Patients who receive another antibacterial drug while on study drug should be considered failures at the time the second antibacterial drug is administered unless a second unrelated infection has been documented and it is known that the second antibacterial drug does not have activity against pathogens known to cause ABS.

d. Other analyses of interest and secondary endpoints

Sponsors can present secondary analyses on variables such as:

- Clinical response based on the number of sinuses involved (e.g., isolated maxillary disease compared to maxillary disease with other sinuses involved).
- Clinical response in unilateral versus bilateral disease.
- Investigator assessment of patient response.
- Subgroup analyses based on patient demographics.

Analyses of secondary and additional endpoints usually should be considered exploratory since a trial usually is not designed to address the questions raised by these analyses, either because of multiple comparisons and/or concerns with subgroup analyses (see section III.B.11., Statistical Considerations). However, the conclusions of such analyses can be strengthened if hypotheses related to these endpoints are prespecified in the protocol, if adjustments for multiple comparisons (maintenance of type I error) are outlined in the protocol, and if the trial is appropriately powered to determine differences between groups related to these variables. Analyses of secondary and additional endpoints can be most helpful for identifying areas for study in future trials.

e. Microbiological response

Although microbiological outcome provides useful information regarding the biological activity of antimicrobials, microbiological outcome is not a direct measure of benefit to patients and, therefore, should be viewed as supportive but not substituting for clinical outcome in a specific trial.

The recommended definitions for microbiological response are as follows:

- Documented negative culture at follow-up equals microbiological success.

- Documented positive culture at follow-up or at time of evaluation equals microbiological failure.
- Documented positive culture more than 48 hours after a previously documented negative culture equals recurrence.

If follow-up cultures are obtained from patients, the cultures can be most useful if samples are obtained after the completion of drug therapy since cultures obtained while on therapy may represent suppression rather than elimination of organisms. Techniques such as placement of a small-bore sinus catheter may allow serial sampling of bacteria from the sinuses. Although information from repeat sinus punctures can be valuable if they are performed, we recognize that repeat sinus punctures on patients who are clinically well may not be acceptable; accordingly, follow-up microbiological data are likely to be incomplete and unable to fully characterize the concordance of clinical and microbiological outcomes.[10] However, we recommend that investigators perform repeat sinus punctures in patients who are clinical failures to document bacteriological failure and evaluate the susceptibility profile of any pathogens isolated. Anaerobic cultures also should be performed on specimens from patients failing initial therapy.

The possibility that there may be a proportion of patients who are clinically cured but who still have positive sinus cultures for bacteria calls into question the use of the outcome categories based on inferred microbiological outcomes such as *presumed microbiological eradication*. Such analyses do not add to what is already known from analyses of clinical outcomes; therefore, there are no recommendations for *presumed eradication* in this guidance. The term *eradication* also may be inaccurate, as bacteria may be present but below the level of detection of culture testing; therefore, the term *no growth on culture* is considered to be more accurate.

10. Study Visits and Timing of Assessments

a. Entry visit

At entry, the investigator should evaluate the patient by performing an appropriate history and physical examination. Information recorded on the case report form during the entry examination should include the following.

- **History and demographic characteristics**

  - Date of visit
  - Age and sex
  - Underlying medical conditions, if any
  - History of previous episodes of acute sinusitis and history of allergic rhinitis
  - History of tobacco use
  - History of smoking
  - Previous or current use of antibacterial drugs, and the indication or reason for use
  - Recent and/or current use of nonantibacterial concomitant medications

[10] Although serial microbiological samples may be more common in studies that perform endoscopy at baseline, these samples may still be incomplete.

598
599 • **Symptoms**
600
601 The presence of each symptom, as discussed in section III.B.2., Study Population, and
602 section III.B.3., Study Inclusion Criteria, should be documented directly as reported by
603 the patient (or caregiver). Baseline symptoms also can be recorded by patients or
604 caregivers in a validated diary (i.e., a PRO or caregiver reporting tool).
605
606 • **Signs**
607
608 – Vital signs including body temperature measurement
609 – Presence of unilateral or bilateral disease
610 – Findings on transillumination of sinuses
611 – Findings on nasal speculum examination
612 – Presence of purulent secretions
613 – Radiographic testing by plain radiographs, computed tomography, or ultrasound
614 – Other laboratory tests (e.g., peripheral WBC count)
615
616 • **Sample collection**
617
618 It is strongly recommended that the entry visit include baseline sinus puncture with
619 culture of the aspirate and identification and susceptibility testing of bacterial isolates
620 recovered from the aspirate. All isolates considered to be possible pathogens should be
621 saved in the event that additional testing of the isolate is needed. For microbiological
622 assessment, the investigator should collect the following information:[11]
623
624 – Identification of the affected sinuses sampled (right and/or left).
625 – A description of how the sample was obtained, processed, and transported to the
626 laboratory.
627 – Identification of the bacterial isolate (this information should remain blinded while
628 the patient is receiving study medication).
629 – In vitro susceptibility (preferably minimum inhibitory concentration) testing of the
630 isolates to both the study and control drugs. This information should remain blinded
631 while the patient is receiving study medication. In vitro susceptibility testing should
632 be performed by using standardized methods, such as the Clinical and Laboratory
633 Standards Institute methods, unless otherwise justified.
634
635 Quantification of the bacterial load at baseline may be helpful for analysis but is not
636 required. If bacterial quantification will be used, the protocol for quantification should be
637 provided to the FDA for review before initiating clinical trials.
638

[11] Similar procedures should be followed if endoscopy is performed as part of the protocol.

b. On-therapy visits

Each patient should have daily on-therapy assessments of symptoms. These assessments can be performed by the investigator during a visit to the investigator's office, by telephone, or by a validated PRO instrument such as a patient or caregiver diary. Regardless of how the assessment is conducted, the questioning of patients or caregivers should be performed in a reproducible and structured way so that any potential biases in the method of questioning do not affect study outcome.[12] The ability to detect differences between study therapies for a time-to-resolution endpoint may be increased if assessments are done more often (e.g., twice daily). Therapy should be continued as described in the study protocol regardless of whether symptoms have resolved; however, patients with resolution of symptoms can be considered as having achieved clinical success if this is a study-defined outcome (i.e., patients with continuing symptoms should be classified as not having achieved clinical success at the measured time point). Investigators should attempt to allow a minimum of 72 hours on therapy with the study medication before classifying a patient as a clinical failure.

Assigning clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening on their assigned treatment arm; specific criteria to identify these patients should be included in the protocol. It is important that investigators distinguish patients who are worsening (i.e., where rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success at a later time point.[13] Sinus puncture can be performed in patients whose therapy has failed and the sample sent for culture and identification and susceptibility testing of isolates. In the case of clinical failure, therapy should then be changed to an appropriate alternative antimicrobial treatment for ABS, with other therapeutic modifications as necessary; results from baseline cultures (if available) can be released to the investigator at this time to guide treatment, although blinding to original treatment arm should still be maintained.

Investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the case report form. If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a validated diary is used to capture patient symptoms during this study, this information also should be recorded on the case report form.

c. Early follow-up visit

The early follow-up visit should occur after completion of all study medication at a time when the drug is expected to clear from the site of infection. For example, if a study drug with a short half-life is administered for 10 days, this study visit can occur on day 10 to 14 after initiation of

[12] See note 8, supra.

[13] In a time-to-resolution analysis, a patient should be classified as a success at the time of complete resolution of symptoms. Although the patients that remain are failures at each time point, failure is not carried forward unless a patient has reached a specific failure endpoint (e.g., the need to alter study treatment for rescue therapy). Criteria for failure or the need for rescue therapy should be explicitly outlined in the clinical protocol. Patients should not be unblinded if a criterion for rescue therapy is met.

therapy. At this visit the investigator should perform a directed medical history and physical examination, as well as appropriate laboratory measurements. The investigator also should inquire about adverse events. Evaluation of relapse is discussed in section III.B.9., Efficacy Endpoints. If clinical failure or relapse is suspected, a specimen should be obtained for bacterial culture, preferably by sinus puncture and aspiration.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all study medication (e.g., if study drug is administered for 10 days, this assessment can occur on days 20 to 24 after initiation of therapy (unless a drug with a long $t_{1/2}$ has been studied)). For patients with no adverse events noted at the early follow-up assessment and who are clinical successes (i.e., previous resolution of all symptoms), this assessment can be performed by a telephone contact. For patients with adverse events occurring at or after the early follow-up assessment, investigators should perform an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, identification of any new adverse events, and follow-up on unresolved adverse events. All adverse events should be followed to resolution. The follow-up assessment should include questions regarding any symptoms of ABS to ascertain if late relapse or late recurrence has occurred; if clinical failure or relapse is suspected, a specimen should be obtained for bacterial culture, preferably by sinus puncture and aspiration.

e. Safety evaluations

The protocol should clearly specify the methods to be used to obtain safety data during the course of the study. Both adverse event information and safety laboratory data should be collected during the study. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations also may be needed because of the preclinical and clinical profile of the specific drug under study (e.g., additional electrocardiogram measurements). Longer-term assessment of adverse events after discontinuation or completion of the antimicrobial also can be considered depending on the specific drug being studied.

All patients should be evaluated for safety at the time of each study visit or assessment, regardless of whether the test drug has been discontinued.[14] All adverse events should be followed until resolution, even if time on study would otherwise have been completed.

11. Statistical Considerations

Sponsors should designate the hypotheses to be tested before initiation of the trial. These hypotheses should be clearly stated in the statistical analysis plan and the trial should be powered to detect differences between study arms. If sponsors choose to test multiple hypotheses, they should address issues related to the potential increase in obtaining false positive results (type I error) because of multiple comparisons, either by adjusting the type I error or using a stepwise,

[14] For specific safety reporting requirements during clinical trials, see the ICH guideline for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (http://www.fda.gov/cder/guidance/index.htm).

closed testing strategy for hypothesis testing. If sponsors use a closed testing hypothesis strategy, they should justify the order of hypothesis testing before initiation of the trial. These issues should be discussed with the FDA in advance of enrollment in the trial.

a. Analysis populations

The following definitions apply to various populations for analyses in ABS clinical trials:

- **Safety population —** All patients who receive at least one dose of assigned therapy during the study.

- **Intent-to-treat (ITT) population** — All patients who are randomized.

- **Modified intent-to-treat (MITT) population (also sometimes referred to as microbiological intent-to-treat population) —** When sinus aspiration or endoscopy is performed for all patients as defined in the study protocol, all patients who are randomized and who have a pathogen known to cause ABS isolated at baseline. Patients should not be excluded from this population based upon events that are measured post-randomization (e.g., loss to follow-up).

- **Per-protocol populations (also referred to as the *clinically evaluable* or *microbiologically evaluable* populations) —** The population of patients who meet the definition for the primary analysis population (ITT or MITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of study medication). Traditionally, adequacy of therapy for a per-protocol analysis population has been defined as patients who have received greater than 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or dosing regimen. Sponsors should document compliance with dosing (e.g., daily assessment, patient or caregiver diary, urine testing, or MEMS caps).

The ITT populations in the study should be evaluated as well as the population of patients who follow important aspects of the protocol (i.e., the per-protocol populations) to ensure consistency of results. However, it is also important to note that the per-protocol population analyses are subgroup analyses since they exclude patients based upon events that occur after randomization. Patients in such subgroup analyses may differ by important factors (both measured and unmeasured) other than the drug received; because of this, analyses based on the ITT (or MITT) population should be considered the primary study analyses, with analyses based on a per-protocol population reviewed for consistency of results. Results in both populations should provide evidence of effectiveness.

For studies where sinus puncture or endoscopy is planned, the population of greatest interest should be patients with a microbiological pathogen identified at baseline since this is the population most likely to show an effect of antibacterial treatment. These studies should be

765 statistically powered for analysis of the MITT population as the primary study analysis rather
766 than the ITT population.[15]
767
768 b. Noninferiority margins
769
770 FDA review of previous ABS studies has not been able to establish a reliable estimate of the
771 magnitude of benefit for treatment of ABS by antimicrobials; because of this, noninferiority
772 trials are currently not considered adequate to establish evidence of effectiveness for regulatory
773 approval of a new indication for ABS. See also the draft guidance for industry *Antibacterial*
774 *Drug Products: Use of Noninferiority Studies to Support Approval*.[16]
775
776 c. Sample size
777
778 The appropriate sample size for a clinical trial should be based upon the number of patients
779 needed to answer the research question posed by the study. The sample size is influenced by
780 several factors including the prespecified type I and type II error rates, the expected success rate,
781 and the noninferiority margin (for a noninferiority trial) or the amount by which the study drug is
782 expected to be superior to the control in a superiority trial. Sample size should be based upon the
783 number of patients needed to draw conclusions in the ITT (no puncture or endoscopy performed)
784 or MITT analysis population.
785
786 d. Missing data
787
788 There is no single optimal way to deal with missing data from clinical trials. Sponsors should
789 make every attempt to limit loss of patients from the trial. Analyses that exclude patients are
790 subgroup analyses, and patients who do not complete the trial may differ substantially from those
791 patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors
792 should prespecify in the protocol the method of how missing data will be included in the analysis
793 of trial results. Sponsors also should present sensitivity analyses in the final study report such as
794 including all missing patients as failures, including all missing patients as successes, and
795 including all missing data as successes or failures in each study group respectively.
796
797 Different rates of missing data or differences in the reasons for missing data across treatment
798 arms can be a cause for concern in the interpretation of a clinical trial. If this situation occurs, it
799 should be addressed in the study report.
800
801 e. Interim testing
802
803 Usually, data and safety monitoring boards (DSMBs) are used to evaluate ongoing safety and
804 efficacy issues during clinical trials of diseases with endpoints that measure mortality and/or

[15] The culture results (i.e., the specific bacterial organisms) that define whether a patient should be included in the MITT population should be stated in the protocol. For example, a study design with all isolates obtained by endoscopy may wish to include only patients with *S. pneumonia* or *H. influenzae* isolates in the MITT analysis to improve specificity.

[16] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

serious morbidity; however, since these endpoints are uncommon in ABS studies, a DSMB may not be needed for an ABS study. If a DSMB is used, a detailed charter with the composition of the committee members and the operational details should be provided for review.[17]

If interim (or futility) analyses will be performed, they should be specified in the analysis plan. Study data also should be examined at the time of interim analysis for any emerging safety signals. We encourage sponsors to discuss their plans with the review division before initiation of the trial to ensure that the overall study significance tests properly address the effect of interim testing.

f. Statistical analysis plan

The sponsor should submit the statistical analysis plan for any phase 3 ABS study to the FDA before initiation of the trial.

Clinical and microbiological outcomes from blinded studies also can be used for assessing the accuracy of an established or tentative microbiological breakpoint for the treatment under study.

C. Other Considerations

1. Labeling Considerations

The following is an example of a labeled indication for the treatment of ABS.

> "Drug X is indicated in the treatment of acute bacterial sinusitis due to susceptible isolates of (insert relevant pathogens based on trial results)."

2. Antimicrobial Resistance Claims

To date, the FDA has not granted resistance claims for ABS. To obtain a claim for resistant pathogens in ABS, sponsors should present data from within their clinical trials to demonstrate the clinical effect of in vitro resistance in this disease. Resistance claims should be relevant to bacterial sinusitis (e.g., amoxicillin resistance is more clinically relevant than penicillin resistance in ABS since amoxicillin is more commonly prescribed for ABS).

[17] For more detailed guidance, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (http://www.fda.gov/cder/guidance/index.htm).