
Guidance for Industry

Acute Bacterial Sinusitis: Developing Drugs for Treatment

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

**October 2012
Clinical Antimicrobial**

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Guidance for Industry¹ Acute Bacterial Sinusitis: 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 drugs² for the treatment of acute bacterial sinusitis (ABS). 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.”

Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of ABS. 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.

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 *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.³

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

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 We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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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.⁴ These discussions have focused primarily on trial designs for ABS and other important issues such as the following:

- 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
- Noninferiority and superiority trial designs

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

New drugs being studied for ABS should have nonclinical data documenting activity against the most commonly implicated pathogens associated with ABS (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*). Animal models of ABS have been developed, particularly for *S. pneumoniae* infection, and pathological and histological responses to antibacterial treatment have been shown in animals. Although these models may contribute to the scientific understanding of ABS and its treatment, the results should be carefully interpreted when being used to help design subsequent human trials. Because clinical trials can be conducted in patients with ABS, animal studies cannot substitute for the clinical trials that must be conducted to evaluate drug safety and efficacy.⁵

⁴ 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 trials for ABS in the context of a specific drug (see <http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective>). In a December 2006 joint meeting of the AIDAC and the Drug Safety and Risk Management Advisory Committee, the issue of noninferiority trial design was discussed in the context of evaluating the risk-benefit profile of a drug. In this case, three indications were under discussion: ABS, acute bacterial exacerbation of chronic bronchitis, and community-acquired bacterial pneumonia (see <http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective>).

⁵ 21 CFR 314.600 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.600>)

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2. Drug Development Population

As previously noted, 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.” This guidance also considers ABS to be restricted to maxillary disease with or without involvement of other sinuses, which is the most common presentation of ABS. 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. Sponsors should discuss with the FDA if patients with maxillary ABS and concurrent nonmaxillary ABS are being considered for clinical trial enrollment.

In addition, although the medical literature commonly refers to disease of the sinuses in conjunction with nasal symptoms as *acute rhinosinusitis*, we consider rhinitis and sinusitis to be distinct disease entities. The administration of antimicrobial drugs is appropriate only for study of bacterial infection of the sinuses. Rhinitis symptoms without sinus disease are most commonly caused by viral infection, allergic rhinitis, and/or vasomotor instability. Because we have approved nonantimicrobial drugs specifically for rhinitis symptoms alone, it is important to separate the effect of antimicrobial therapy on ABS from treatment of nasal symptoms caused by nonbacterial sources.

3. Efficacy Considerations

We have not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABS with antimicrobial drugs from reviewing previous ABS trials. Such an estimate would be a precondition for a noninferiority trial. Accordingly, we recommend only superiority trials for ABS.

The goal of ABS clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABS caused by *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. 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. For example, some trials have implicated *Staphylococcus aureus* as a pathogen in ABS in a setting where this has been the sole pathogen isolated. Sponsors should discuss with the FDA during drug development the methods to provide data on relevant bacterial pathogens that cause ABS. For example, microbiological data can be obtained by one or more of the following approaches: (1) baseline sinus puncture and aspiration (or endoscopy) performed on all patients enrolled in the phase 3 trial (see section III.B.5.b., Baseline sinus aspiration and endoscopy); (2) a subset of patients who have baseline sinus puncture and aspiration (or endoscopy) performed in the phase 3 trial; (3) baseline sinus puncture and aspiration (or endoscopy) performed on patients enrolled in a phase 2 trial; or (4) microbiological data obtained during clinical development of the investigational drug for treatment of another infectious disease in which the bacterial pathogens are identical or similar to bacterial pathogens known to cause ABS.

The number of trials needed for approval of an ABS indication depends on the overall development plan for the drug under consideration. If the development plan for a drug has ABS

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as the sole marketed indication, we recommend that two adequate and well-controlled trials establishing safety and efficacy be conducted for this indication.

A single trial for an ABS indication may be appropriate if: (1) there are data from other clinical trials demonstrating effectiveness in other respiratory tract diseases; and (2) 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 bacterial pneumonia (CABP) trials may be supportive of a single superiority trial of ABS because of the similar microbiology and greater seriousness of CABP relative to ABS.

The disease course and treatment for ABS is of a short-term duration. Direct assessment of ABS symptoms to support a conclusion of treatment benefit in response to antibacterial drug therapies is readily measured. As such, there are no surrogate markers accepted by the FDA. 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

Antimicrobial drugs 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 trials 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, 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. This can be accomplished either by enhancing clinical trial enrollment to arrive at a sufficient sample size for safety evaluations or by enrolling an appropriate number of patients in another trial designed to evaluate safety. 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. Clinical Trial Design

Currently, we recommend only superiority trials for ABS. 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 trial initiation. This situation is discussed further in section III.B.12., Statistical Considerations.

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

- **Placebo-controlled trial with a background of best available nonantimicrobial therapy** — This design tests the safety and efficacy of an investigational antimicrobial drug as an addition to a standardized regimen of the best available analgesic and decongestant medications compared to the same standardized regimen plus placebo.
- **Dose-response** — Patients in each arm receive different antimicrobial drug doses (or dosing regimens) for which there is equipoise together with a standardized regimen of the best available 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 investigational antimicrobial to another antimicrobial** — Patients in one arm receiving the investigational drug (with standardized regimen of the best available background nonantimicrobial therapy) are compared with patients in a control arm receiving another antimicrobial drug (with standardized regimen of the best available background nonantimicrobial therapy). To demonstrate efficacy, the arm receiving the investigational antimicrobial drug should demonstrate superiority to the arm receiving the control antimicrobial drug.

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

ABS trials should be parallel group designs, because crossover designs may be subject to carry-over and period effects. Other trial designs to demonstrate superiority can be discussed with the FDA.

2. Trial Population

ABS trials should include patients of both sexes and all races. 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. If it is feasible to perform sinus puncture and aspiration, documenting the presence of bacteria in the sinus cavity can be an important means of enriching the trial population for analysis, and can also serve to confirm that enrollment procedures have succeeded in enrolling 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 a history of symptoms for a minimum of 7 to 10 days before enrollment, without improvement over the 3 days immediately before enrollment.

An alternative trial 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

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improved over the 3-day run-in period may enrich the trial population for patients with a bacterial etiology of sinusitis.

We do not recognize different forms of ABS based on disease severity at presentation. However, we recognize that investigators in a placebo-controlled trial may be less likely to enroll patients presenting with *severe* disease than patients with milder symptoms, and that enrollment of hospitalized patients may be incompatible with a placebo-controlled trial. Current practice guidelines state the following conclusions and research needs: “More placebo-controlled RCTs [randomized clinical trials] that incorporate both pre- and posttherapy [sic] sinus cultures and a clinical severity scoring system are urgently needed to provide critical information regarding the natural history of ABRs [acute bacterial rhinosinusitis] as well as the timeliness and efficacy of antimicrobial therapy.”⁶ If sponsors wish to study patients with severe disease (or hospitalized patients), we strongly encourage discussion with the FDA regarding protocol design and adherence to current practice guidelines.

3. *Inclusion Criteria*

a. Symptoms

At least two of the following symptoms should be present in patients with ABS:

- Maxillary tooth pain (unilateral findings can be more specific)
- Facial pain (unilateral findings can be more specific)
- Frontal headache
- Purulent nasal discharge (unilateral findings can be more specific)
- New onset fetor oris (bad breath)
- Morning cough
- Nasal obstruction

b. Signs

At least one of the following signs should be present in patients with ABS:

- 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:

⁶ Chow, AW, MS Benninger, I Brook et al., 2012, IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults, *Clinical Infectious Diseases*, doi: 10.1093/cid/cir1043, published March 20 2012, ahead of print.

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- Fever (e.g., temperature greater than or equal to 38 degrees Centigrade)
- Malaise

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). If baseline sinus puncture and aspiration is performed in the trial, the radiographic findings may help to guide the sinus puncture and aspiration procedure (see section III.B.5.b., Baseline sinus aspiration and endoscopy), which enhances the ability to identify a bacterial pathogen on culture.

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 pathogens⁷
- Patients with cystic fibrosis
- Immunocompromised patients or patients with other medical conditions that may affect interpretation of the effect of trial drugs
- Patients who are allergic to any of the trial drugs
- Patients with nasal polyposis

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

⁷ If sponsors plan to include patients with maxillary sinusitis and evidence of concurrent frontal, sphenoidal, or ethmoidal sinusitis, they should discuss with the FDA the enrollment criteria and efficacy evaluation before trial initiation.

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5. *Additional Clinical Trial Entry Procedures*

a. Radiography

Previous evaluations 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, we strongly recommend radiological assessment as a means to enrich the trial population. In clinical trials, the number of patients who are screened for enrollment but then have negative radiography should be recorded and included in the trial report. The clinical characteristics of patients screened but not enrolled also should be recorded.

b. Baseline sinus aspiration and endoscopy

A microbiological diagnosis of ABS can be confirmed by isolating a bacterial pathogen from a specimen obtained by maxillary sinus puncture at baseline. If sinus puncture and aspiration is performed in the trial, Gram stain of the aspirate material with examination for white blood cells (WBCs) should be performed, as well as in vitro antimicrobial susceptibility testing of bacterial isolates.

Sponsors considering endoscopic cultures at baseline should discuss this with the FDA in advance of trial initiation.

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

If baseline sinus puncture or endoscopy is performed, the trial should be conducted at sites with expertise in the procedure. The protocol should describe the specific methods to be used for obtaining, transporting, and processing specimens and should describe specific culture techniques to be used on specimens.

6. *Randomization, Stratification, and Blinding*

Patients should be randomized for treatment assignment at enrollment. All trials should be double-blinded for therapy and assessment of outcome.

When microbiological sampling is performed, investigators should be blinded to the microbiological data obtained at entry. If patients fail therapy and require rescue therapy, the results of baseline and any subsequent microbiological data should be made available promptly to the treating clinician.

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7. *Special Populations*

Sponsors will likely be required to conduct trials to support labeling for use in the pediatric population.⁸ Pediatric patients 1 year old and older can be included along with adults in ABS trials 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 trials. Sinus puncture may not be appropriate for pediatric patients in certain situations. Sponsors should discuss with the FDA when sinus puncture in pediatric patients is planned, before trial initiation, 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, including the potential for extrapolation of adult efficacy data, appropriate pharmacokinetic studies in pediatric patients to support the selection of the dose, and preapproval of a safety database in children.

Drug development programs should include a sufficient number of geriatric patients to characterize safety and efficacy in this population. Patients with renal or hepatic impairment can be enrolled provided pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

8. *Dose Selection*

Selection of an appropriate dose and duration of therapy for phase 3 clinical trials should use information gathered in earlier clinical development; for example, data from pharmacokinetic and pharmacodynamic studies (including information regarding sinus penetration of the drug) and data from phase 2 dose-ranging trials.

9. *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 nonantimicrobial therapies between trial groups. Such confounding may occur even if the number of patients receiving concomitant medications is similar between treatment 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.

⁸ The Pediatric Research Equity Act (Public Law 108-155) requires the conduct of pediatric studies for certain drug and biological products (see section 505B(b) of the Federal Food, Drug, and Cosmetic Act). See the draft guidance for industry *How to Comply With the Pediatric Research Equity Act*. 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 Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications.

Treatment groups should be well-balanced with the use of nonantimicrobial therapies to ensure that the treatment effect on an outcome measure would be attributed to the investigational antibacterial drug. 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 trial.

Concomitant medication use should be captured in all patients using a daily medication log. Use of concomitant medications alone should not be an efficacy endpoint but should be analyzed in combination with a symptom assessment using a patient-reported outcome (PRO) or caregiver-reported instrument. For example, the endpoint can be defined to evaluate whether symptoms persist after concomitant medication administration.

10. Efficacy Endpoints

The primary emphasis of the trial should be the effect of the antimicrobial drug on outcomes that are clinically important to patients. A well-defined and reliable PRO measure designed to capture the important symptoms of ABS can be considered a direct measure of treatment benefit and can be used in a trial to support labeling claims for efficacy. Patient outcome should be based on symptom response per patient rather than per sinus (i.e., outcome is measured identically regardless of whether unilateral or bilateral disease is present). The primary outcome assessment can be characterized as a *success* or *failure* as follows:

- *Clinical success.* Clinical success can be documented when a patient reports improvement or 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:
 - Protocol-defined worsening of symptoms or failure to improve at certain time points (e.g., failure to have symptomatic improvement 72 hours after treatment onset)
 - Development of a new symptom of ABS during treatment
 - 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
 - Treatment with nontrial antibacterial drugs for another related infectious disease (e.g., for treatment of CABP)

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A PRO instrument can measure responses based on a scale score, and then the score should be used as the outcome variable. For patients who cannot report for themselves (e.g., young children), a caregiver assessment can be developed that reports on behaviors and signs that are probably related to the patient's symptoms. Development of a new PRO or caregiver-reported instrument should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.⁹ For example, after content validity is established, sponsors can evaluate construct validity, reliability, and responsiveness of the instrument during phase 2 trials. Evaluation of the patient responses using the instrument in phase 2 could be used to inform sample size calculations for phase 3 trials.

We recommend that the primary efficacy endpoint should be the time to clinical success, defined as the period from the start of trial drug therapy to clinically meaningful symptomatic improvement or resolution. 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.

Patients who experience improvement of symptoms but then worsen during clinical trial participation should be considered clinical failures on the primary efficacy analysis. Sinus puncture in patients who experience additional symptoms may be valuable for secondary analyses, because the results would allow a differentiation between patients who may still harbor the initial pathogen (relapse) compared with those patients who have acquired a new pathogen or have a noninfectious etiology for symptoms (recurrence). Bacterial isolates obtained from clinical relapse or recurrences should be subjected to an appropriate in vitro method (e.g., pulse field electrophoresis gel) to determine if the original isolate and the subsequent isolate are indistinguishable (relapse) or different (recurrence). The susceptibility profile should be performed for any pathogens isolated.

Patients who discontinue therapy because of an adverse event should be evaluated at the time of discontinuation of the trial drug therapy. These patients should not be considered *withdrawn from the trial* in terms of overall evaluation; investigators should continue to follow all such patients at trial visits as scheduled and continue to record information on both safety and efficacy outcomes. If at the time the trial drug therapy 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.

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 the patient's clinical signs

⁹ For more information regarding the development of PRO measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

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- Subgroup analyses based on patient demographics

Analyses of secondary and additional endpoints usually should be considered exploratory because 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.12., 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.

11. Trial 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

- **Symptoms**

The presence of each symptom, as discussed in section III.B.2., Trial Population, and section III.B.3., Inclusion Criteria, should be documented directly as reported by the patient (or caregiver). Baseline symptoms also can be recorded by patients or caregivers in a PRO or caregiver-reported instrument that is well-defined and reliable in the population to be studied.

- **Signs**

- Vital signs including body temperature measurement
- Presence of unilateral or bilateral disease
- Findings on transillumination of sinuses

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- Findings on nasal speculum examination
- Presence of purulent secretions
- Radiographic testing by plain radiographs, computed tomography, or ultrasound
- Other laboratory tests (e.g., peripheral WBC count)

- **Sample collection**

At clinical trial sites where sinus puncture and aspiration will be performed, baseline sinus puncture with aspirate should be sent for culture and identification and in vitro susceptibility testing of bacterial isolates. All isolates considered to be possible pathogens should be saved in the event that additional testing of the isolate is needed. For microbiological assessment, the investigator should collect the following information:¹⁰

- Identification of the affected sinuses sampled (right and/or left).
- A description of how the sample was obtained, processed, and transported to the laboratory.
- Identification of the bacterial isolate (this information should remain blinded while the patient is receiving trial drug therapy).
- In vitro susceptibility (preferably minimum inhibitory concentration) testing of the isolates to both the trial and control drugs. This information should remain blinded while the patient is receiving trial drug therapy. In vitro susceptibility testing should be performed by using standardized methods, such as the Clinical and Laboratory Standards Institute methods, unless otherwise justified.

Quantification of the bacterial load at baseline may be helpful for analysis but is not required. If bacterial quantification will be used, the protocol for quantification should be provided to the FDA for review before initiating clinical trials.

b. On-therapy visits

Each patient should have daily on-therapy assessments of symptoms using a well-defined and reliable PRO or caregiver-reported instrument that ensures that any potential biases in the method of questioning do not affect trial outcome. The ability to detect differences between 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 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 trial-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 trial drug therapy before classifying a patient as a clinical failure.

¹⁰ Similar procedures should be followed if endoscopy is performed as part of the protocol.

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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.¹¹ Sinus puncture can be performed in patients whose therapy has failed and the sample sent for culture and identification and in vitro 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.

Consideration should be given to obtaining blood sample for the measurement of drug concentration (e.g., a sparse sampling strategy). An assessment of drug exposure in phase 3 could help explain trial outcomes related to efficacy and/or safety. It could also be used to assess the relationship between the pharmacokinetic/pharmacodynamic indices and observed clinical outcomes. The protocol should provide a description of the sampling strategy and the proposed analysis plan.

c. Early follow-up visit

The early follow-up visit should occur after completion of all trial drug therapy at a time when the investigational drug is expected to clear from the infection site. For example, if the investigational drug with a short half-life is administered for 10 days, this visit can occur on day 11 to 14 after therapy initiation. 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. If clinical relapse or recurrence is suspected, a specimen should be obtained for bacterial culture 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 therapy (e.g., if trial drug therapy is administered for 10 days, this assessment can occur on days 20 to 24 after therapy initiation). For patients who have 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 or other interactive technology. 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. The follow-up assessment should include questions regarding any symptoms of

¹¹ 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 development of a bacterial complication of ABS and the need to administer rescue therapy). Criteria for failure or the need for rescue therapy should be explicitly outlined in the clinical protocol.

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ABS to ascertain if clinical relapse or recurrence has occurred; if clinical relapse or recurrence is suspected, a specimen should be obtained for bacterial culture.

e. Safety evaluations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. 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 nonclinical and clinical profile of the specific drug under study. 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 trial visit or assessment, regardless of whether the test drug has been discontinued. Although serious and unexpected adverse events and follow-up information about these events are required to be reported (21 CFR 312.32 (c)(1)(i)(A) and 21 CFR 312.32(d)(1) and (2)), we recommend that in general all adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

12. *Statistical Considerations*

Sponsors should designate the hypotheses to be tested before trial initiation. These hypotheses should be stated in the statistical analysis plan and the trial should be powered to detect differences between trial 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, closed testing strategy for hypothesis testing. If sponsors use a closed testing hypothesis strategy, they should justify the order of hypothesis testing before trial initiation. These issues should be discussed with the FDA in advance of trial enrollment.

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 trial.
- **Intent-to-treat (ITT) population** — All patients who are randomized.
- **Microbiological intent-to-treat (micro-ITT) population** — When sinus aspiration or endoscopy is performed as defined in the protocol, 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 after randomization (e.g., loss to follow-up).

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- **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 micro-ITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of trial drug therapy). 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).

In general, the ITT population should be considered the primary analysis population. Trials that enroll patients with baseline sinus aspiration can choose to evaluate the micro-ITT population as the primary analysis population. The micro-ITT population is the population most likely to show the largest treatment effect of antibacterial treatment.¹² Other analysis populations in the trial should be evaluated as well to ensure consistency of results. It is important to note that the per-protocol population analyses are subgroup analyses because 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.

b. Noninferiority margins

FDA review of previous ABS trials has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABS by antimicrobial drugs. Therefore, we do not recommend the use of noninferiority trials to establish evidence of effectiveness for regulatory approval of a new indication for ABS. See also the draft guidance for industry *Non-Inferiority Clinical Trials*¹³ and the guidance for industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the amount by which the investigational drug is expected to be superior to the control (effect size). Sample size should be based upon the number of patients needed to draw conclusions based on the analysis population. For example, the effect size for an antibacterial drug is likely to be larger among patients in a micro-ITT analysis population with confirmed bacterial pathogens. There may be circumstances where a sample size estimate for an efficacy analysis in ABS trials may not include a sufficient number of patients for an adequate evaluation of safety,

¹² The culture results (i.e., the specific bacterial organisms) that define whether a patient should be included in the micro-ITT population should be stated in the protocol. For example, a trial design with all isolates obtained by endoscopy may wish to include only patients with *S. pneumoniae* or *H. influenzae* isolates in the micro-ITT analysis to improve specificity.

¹³ 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 Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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in which case there are several choices to enhance the number of patients in an overall preapproval safety database (see section III.A.4., Safety Considerations).

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from those patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors should prespecify in the protocol the method of how missing data will be included in the analysis of trial results. Sponsors also should present sensitivity analyses in the final report such as including all missing patients as failures, including all missing patients as successes, and including all missing data as successes or failures in each treatment group respectively.

Different rates of missing data or differences in the reasons for missing data across treatment arms can be a cause for concern in the interpretation of a clinical trial. If this situation occurs, it should be addressed in the report.

e. Statistical analysis plan

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

13. Ethical Considerations

Review of previous placebo-controlled trials of the treatment of ABS has shown variable results, with several placebo-controlled trials showing no effect of antimicrobial treatment for ABS. Accordingly, trials have not shown a risk to placebo-treated patients that make future placebo-controlled trials unethical; the risk from placebo treatment may be similar to that associated with antibacterial therapy because 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 antibacterial therapy can be incorporated into the trial design so that individual patients are treated at the time a failure outcome is assigned; this may serve to mitigate concerns regarding inclusion of a placebo group in an ABS trial. All trial designs should provide appropriate provisions for patient safety.

14. 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 (Genus and species of the relevant bacterial pathogens).”