# Guidance for Industry

# Acute Bacterial Otitis Media: Developing Drugs for Treatment

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

**September 2012**
**Clinical Antimicrobial**

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*Contains Nonbinding Recommendations*

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## I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial otitis media (ABOM). This guidance defines ABOM as "the recent or acute onset of inflammation of the middle ear caused by a bacterial pathogen." Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of ABOM.[2]

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] This guidance focuses on specific drug development and trial design issues that are unique to the study of ABOM.

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.

[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.

## II. BACKGROUND

There have been a number of public discussions regarding clinical trial designs for the study of ABOM.[4] These discussions have primarily focused on the appropriateness of endpoints and trial designs for ABOM and other important trial design 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 data
- Noninferiority and superiority trial designs

## III. DEVELOPMENT PROGRAM

### A. General Considerations

#### *1. Early Phase Clinical Development Considerations*

a. Nonclinical studies

New drugs being studied for ABOM should have nonclinical data documenting activity against the most commonly implicated pathogens for ABOM (i.e., *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*).

b. Animal models

Animal models may be useful in demonstrating potential activity in the treatment of ABOM (or in comparing the in vivo activity of different antimicrobials). Pharmacokinetic (PK) and pharmacodynamic data from animal studies may be helpful in the design of subsequent clinical trials, including the selection of doses that will be evaluated in those trials. However, animal studies cannot be considered a substitute for clinical trials. Because clinical trials are ethical and feasible in patients with ABOM, approval cannot be obtained under subpart I.[5]

[4] ABOM clinical trial design was the subject of the July 11, 2002, meeting of the Anti-Infective Drugs Advisory Committee (meeting transcripts are available at www.fda.gov/ohrms/dockets/ac/02/transcripts/3875T2.doc). We also convened a 2011 public workshop titled "Design of Clinical Trials for Systemic Antibacterial Drugs for the Treatment of Acute Otitis Media." Transcripts of the workshop proceedings are available at http://www.fda.gov/Drugs/NewsEvents/ucm262641.htm.

[5] See 21 CFR 314.600, subpart I, Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible.

c. Efficacy outcome measure development

There should be well-defined and reliable methods of diagnosing ABOM and of assessing patient responses in ABOM trials. Sponsors should anticipate the need for appropriate instruments to evaluate responses (e.g., well-developed patient-reported outcome (PRO) or caregiver-reported outcome instrument, or clinician-reported outcome instruments) early in the clinical development process. The development of new instruments should begin in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocols. For example, after content validity is established (a critical step during instrument development that evaluates the extent to which the instrument measures the concepts of interest), other types of validity, reliability, and responsiveness of the instrument can be evaluated during phase 2 trials. Evaluation of the responses using the instrument in phase 2 could be used to inform sample size calculations for phase 3 trials.

PRO instruments can be used to measure patient symptoms and self-reported signs; for young children and individuals who cannot respond reliably for themselves, a caregiver-reported outcome instrument can be used to measure patient signs as observed by the caregiver (observable signs).[6] Both types of instruments may be appropriate for use in a single trial depending on the patient population enrolled. For more information regarding the development of PRO measures or caregiver outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* and the draft guidance for industry *Qualification Process for Drug Development Tools*.[7]

Documentation of clinical signs of ABOM as observed by the clinician is useful for outcome assessments (e.g., a clinician-reported outcome instrument). Sponsors should describe the characteristics of patients with a diagnosis of ABOM and describe objective assessments of the patient's responses to therapy. It is important to distinguish patients with otitis media caused by viral pathogens or allergic conditions from patients with ABOM.

*2. Drug Development Population*

The drug development population should include patients with ABOM, defined as the recent or acute onset of inflammation of the middle ear caused by a bacterial pathogen.

[6] It is important to note how the terms *sign* and *symptom* are used in this guidance in the context of PRO and caregiver-reported outcome instruments. PRO instruments can capture both signs and symptoms reported by the patient. A caregiver-reported outcome instrument by definition is not a PRO, but may be the best option for capturing patient outcomes for younger children who may not be able to directly articulate their subjective state. In a caregiver-reported outcome instrument, pain intensity measurement as experienced by a young child can be inferred and reported by a caregiver based on the child's behavior, in which case it is measured as a *sign* rather than as a true *symptom*. As used in this guidance, the terms *sign* and *symptom* include in most contexts the subjective state of the patient, but *symptoms* can be reported only by the patient. Therefore, where a caregiver-reported outcome instrument is used, the information captured may be limited to observable signs.

[7] When final, this guidance will represent the FDA's current thinking on this topic.

### *3. Efficacy Considerations*

The goal of ABOM clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABOM caused by *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, or other additional bacterial pathogens, provided that data are sufficient to substantiate the clinical relevance of the particular bacterial pathogen as a pathogen in ABOM. During drug development, sponsors should discuss with the FDA the methods they may use to provide data on relevant bacterial pathogens that cause ABOM. For example, microbiological data may be obtained by one or more of the following methods: (1) baseline tympanocentesis in all patients enrolled in a phase 3 trial (see section III.B.3.d., Baseline tympanocentesis); (2) baseline tympanocentesis in a subset of patients in the phase 3 trial; (3) baseline tympanocentesis in 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 that are known to cause ABOM. An advantage of microbiologic confirmation by tympanocentesis is the potential to perform analyses of treatment responses by individual pathogens.

The number of clinical trials that should be conducted in support of an ABOM indication depends on the overall development plan for the drug under consideration. A single trial for an ABOM indication may be appropriate if there are data from other clinical trials demonstrating effectiveness in other respiratory tract diseases and there is additional supportive information, such as PK trials demonstrating concentration of the antibacterial drug in the middle ear fluid at a level expected to be active against the common pathogens causing ABOM.[8]

The disease course and treatment for ABOM is of a short-term duration and the clinical outcome is readily measured. Currently, there are no surrogate markers accepted by the FDA as substituting for clinical outcomes in ABOM trials. Sponsors who wish to propose a surrogate marker for clinical outcome of ABOM should discuss this with the FDA early in the drug development process.

### *4. Safety Considerations*

There should be sufficient evidence of drug safety from ongoing or completed clinical trials of other respiratory infections in adults before ABOM trials are initiated in children, even if ABOM for a pediatric population is the sole indication being pursued by a sponsor. Antibacterial drugs with clinically significant toxicity identified in earlier trials are not considered appropriate for study of this indication.

Drug safety information should be collected from studies of pediatric patients who receive the drug administered at the dose and duration proposed for use. Although it may be possible to derive some safety information from trials of the new drug in adults when exposure is similar to or greater than what is anticipated for treatment of ABOM in children, there also should be sufficient evidence of safety derived from trials in children. The total number of pediatric patients and the distribution by age group (given that ABOM occurs more commonly among

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

children younger than approximately 5 years of age) that are needed to support an ABOM indication should be discussed with the FDA early in the drug development process.

Safety evaluations and assessments should consider the patient populations that are likely to be treated for ABOM. Protocols for ABOM should specify the age-appropriate methods to be used to obtain safety data during clinical trials. Clinical trials should be designed in a manner that facilitates the collection of information to characterize the safety of the experimental drug. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be appropriate 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 drug should be considered depending on the specific drug being studied and the potential for long-term or delayed adverse effects based on, for example, observations from nonclinical toxicology studies, safety data from other clinical trials, or postmarketing safety data, if available.

## B. Specific Efficacy Trial Considerations

### *1. Trial Design*

The type of clinical trial design will depend on the type of patients enrolled in the trial (e.g., age and disease presentation).

#### a. Active-controlled clinical trials

Children for whom treatment with an antibacterial drug is recommended by treatment guidelines from professional societies (e.g., children between 6 months and 23 months of age with severe ABOM)[9] should be enrolled in active-controlled clinical trials. An active-controlled trial can be designed for a finding of superiority or noninferiority. Sponsors planning an active-controlled noninferiority trial should discuss with the FDA the scientific data needed to support selection of a noninferiority margin.[10]

#### b. Placebo-controlled clinical trials

Children for whom either observation (*watchful waiting*) or treatment with an antibacterial drug is recommended by treatment guidelines from professional societies (e.g., children 24 months of age or older without severe ABOM) can be enrolled in placebo-controlled trials. Placebo-controlled trials should include an early assessment at approximately 48 hours that documents clinical signs of ABOM as observed by the clinician with defined objective characteristics of patients with no improvement or progression of disease. Such patients should be offered *rescue* antibacterial drug therapy.

[9] See the most recent treatment guidelines by professional societies (e.g., Subcommittee on Management of Acute Otitis Media, 2004).

[10] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.

*2. Clinical Trial Population*

Clinical trials should enroll male and female children with ABOM.

*3. Entry Criteria*

The minimum subset of specific signs and symptoms needed for enrollment should be defined in the protocol as part of the inclusion criteria for the trial. The inclusion criteria should be selected to yield a strong likelihood that a patient has disease attributable to a bacterial pathogen. A protocol also can specify different criteria for the diagnosis of ABOM for different age groups if this improves the overall positive predictive validity for bacterial disease. A combination of signs and symptoms, including fever with yellow or red bulging tympanic membrane, irritability, and ear tugging, has been associated with a tympanocentesis culture demonstrating the presence of a bacterial pathogen (Rodriguez and Schwartz 1999; Leibovitz, Satran, et al. 2003). The following information may be used in the selection of appropriate inclusion criteria.

a. Patient history and characteristics

The following patient demographic characteristics should be used to provide a better chance of selecting patients likely to have bacterial disease:

- Younger ages (e.g., younger than approximately 5 years)

- Biphasic illness: acute onset (24 to 48 hours) of ABOM symptoms preceded by predisposing infections, such as rhinitis, pharyngitis, and tonsillitis

b. Symptoms and observable signs

Infants and younger children often present with nonlocalizing observable signs of otitis media; older children may be more likely to articulate symptoms referable to the ear.

Signs that may be observed in infants and younger children include the following:

- Head rolling
- Ear tugging
- Ear rubbing
- Fussiness or irritability
- Inconsolability
- Decreased appetite
- Sleep disturbance

Symptoms that may be measured in older children with ABOM include the following:

- Ear pain or earache
- Ear fullness
- Decreased hearing

c. Clinical signs

The following bullet points provide a general framework for defining clinical signs for the protocol and for deciding whether to include them as part of the entry criteria.

- Clinicians with experience in otoscopy should be able to identify patients who have ABOM. Otoscopic findings considered consistent with ABOM include:

  - Bulging or fullness of the tympanic membrane (convexity of the plane of the eardrum), with loss of anatomic landmarks on visualization

  - Opacification of the tympanic membrane regardless of color

  - Erythema of the tympanic membrane

  - Abnormal tympanic membrane mobility on biphasic pneumatic otoscopy; a tympanic membrane in the neutral position or retracted is not sufficient evidence of ABOM because these findings are not specific enough to distinguish the disease from otitis media with effusion

- Photography or videography can be performed and evaluated centrally for findings consistent with ABOM

- The results of tympanometry and/or electroacoustic reflectometry can be used to define entry criteria and help select patients to undergo tympanocentesis, if this procedure is planned in the clinical trial

- Other clinical signs of ABOM may include the following:

  - Elevated body temperature (e.g., temperature greater than 38 degrees Celsius)
  - Elevation in peripheral white blood cell (WBC) count

d. Baseline tympanocentesis

If tympanocentesis is included in a trial, sponsors should ensure that the individuals at these centers have sufficient experience and training to perform tympanocentesis. When tympanocentesis is performed, Gram stain of the aspirate material with examination for WBC count also should be performed, with culture as well as antimicrobial susceptibility testing of all bacterial isolates.

e. Exclusion criteria

The following patients should be excluded from trials for the treatment of ABOM:

- Patients with otitis externa

- Patients with tympanostomy tubes at the time of trial entry[11]
- Immunocompromised patients or patients with other medical conditions that may affect interpretation of the effect of investigational drugs
- Patients on any medications that may affect the interpretation of trial outcome (e.g., inhaled steroids)
- Patients with craniofacial abnormalities
- Patients with concomitant infections other than ABOM that may influence the assessment of drug efficacy and safety
- Patients who are allergic to any of the investigational drugs
- Patients with erythema of the tympanic membrane without other evidence of otitis media[12]

For noninferiority trials, patients who have received antimicrobial therapy for the current episode of ABOM may bias the results toward a finding of noninferiority. Thus, we recommend exclusion of patients who received prior antibacterial drug therapy from noninferiority trials. For superiority trials, receipt of prior antibacterial drugs for the current episode of ABOM can be permitted.

*4. Randomization, Stratification, and Blinding*

Patients should be randomized for receipt of investigational drugs at enrollment. All trials should be double-blinded for trial therapy and assessment of outcome.

We recommend stratification by age because younger patients (i.e., younger than 2 years of age) may have lower cure rates than older patients. Other possible stratification factors include unilateral versus bilateral disease, and the presence or absence of otorrhea.

*5. Dose Selection*

The pharmacokinetics of the drug in children, including any changes in pharmacokinetics with age, should be established before initiating efficacy trials in children.[13] Initial dose selection

[11] Patients with an acute, recent tympanic membrane perforation related to the present episode of ABOM can be enrolled if other entry criteria are met.

[12] Although nonspecific as an isolated finding, the absence of diffuse erythema has a relatively high negative predictive value for ABOM.

[13] For guidance on the PK information needed to select appropriate doses for the pediatric population, see the draft guidance for industry *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*. When final, this guidance will represent the FDA's current thinking on this topic.

may be made based on a single-dose PK trial in children. The single-dose trial may include dose adjustments to achieve the desired exposure that is anticipated to provide efficacy. After sufficient data are available to select an appropriate dose and duration for the investigational drug, an efficacy trial can include a population PK approach to supplement the single-dose PK data. PK data in combination with efficacy and safety data from phase 2 dose-ranging trials contribute to the selection of an appropriate dose and duration for phase 3 clinical development. Data from phase 2 trials with tympanocentesis demonstrating drug penetration into middle ear fluid can also inform dose selection for subsequent trials.

*6. Choice of Comparators*

In an active-controlled trial, the control antibacterial drug should be FDA-approved for treatment of acute otitis media (AOM) or treatment of ABOM and recommended for treatment in guidelines published by professional societies.

*7. Concomitant Medications*

The protocol should specify the use of effective analgesia for pain associated with ABOM. We discourage the use of antihistamines or decongestants. If other treatments are permitted in the trial, their use should be standardized across treatment groups. Because concomitant medications may have an effect on outcome assessments and introduce confounding, the use of concomitant medications should be well-balanced between the treatment groups to ensure that the observed treatment effect is caused by the investigational drug.

*8. Efficacy Endpoints*

The primary efficacy endpoint of the clinical trial should evaluate the effect of the antimicrobial drug on clinically important patient symptoms and functioning. A parent- or caregiver-reported outcome instrument can be used as a primary efficacy endpoint if it is well-defined and reliable. It may be helpful to evaluate symptom improvement based on measurements at time points early in therapy, which may have greater sensitivity to treatment differences of an antibacterial drug. However, the amount of improvement determined to be clinically meaningful (and, therefore, appropriate for regulatory decisions) should be determined during clinical development and discussed with the FDA before trial initiation.

A primary efficacy endpoint can be a binary response of clinical success or failure where response criteria are prespecified and are based upon measurements obtained using well-defined and reliable outcome assessment tools. The primary efficacy endpoint can be evaluated as the time to clinical success or evaluated at a fixed time point (e.g., a fixed time point early in the course of therapy).

- *Clinical success.* Clinical success can be documented when a patient exhibits improvement (or resolution) of disease-specific symptoms and observable signs present at enrollment (e.g., head rolling, ear tugging, ear rubbing), and the absence of new symptoms or observable signs attributable to ABOM.

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

  – Development of complications of ABOM such as mastoiditis

  – Lack of improvement or worsening of disease-specific clinically meaningful symptoms or observable signs

  – The development of new symptoms or signs attributable to ABOM

  – Treatment with rescue nontrial antibacterial drugs for ABOM

  – Treatment with nontrial antibacterial drug for another infectious disease, and the antibacterial drug has activity in the treatment of ABOM

Patients designated as clinical failures at an early time point should also be designated as clinical failures for all subsequent follow-up visits.

*9. Trial Procedures and Timing of Assessments*

a. Entry visit

At entry, the investigator should evaluate the patient by performing an appropriate history and physical examination, as follows:

- **History and demographic characteristics**

  – Date of visit

  – Age, sex, and weight

  – Underlying medical conditions, if any

  – Current medications, if any

  – History of allergies or allergic symptoms

  – Social environment (e.g., day care attendance), including smoke exposure

  – Number of distinct and well-documented episodes of AOM/ABOM in the previous 12 months and how this information is obtained (i.e., chart review or recall of caregiver); dates, treatment regimens, and outcomes should be recorded

- **Symptoms and observable signs**

  The presence of each symptom should be documented directly as reported by the patient using a PRO assessment. If patients cannot report for themselves, symptom assessment

is not possible. A caregiver can provide information about observable signs that may indirectly assess symptoms using a caregiver-reported outcome assessment.

- **Clinical signs at clinic visit**

  - Vital signs, including body temperature measurement.

  - Presence of unilateral or bilateral disease.

  - Otoscopic findings for each ear, including position of tympanic membranes, color, and mobility on pneumatic otoscopy. The absence of tympanic membrane perforation for each ear should be documented.

  - Tympanometry and/or electroacoustic reflectometry for each affected ear.

  - Other laboratory tests as appropriate (e.g., peripheral WBC count).

For trials where microbiological information is being obtained by baseline tympanocentesis, the middle ear fluid should be sent for culture and in vitro susceptibility testing of any bacteria isolated. 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:

- Identification of the affected ear sampled (i.e., right or left).

- A description of how the sample was obtained, processed, and transported to the laboratory.

- Identification of the bacterial isolate.

- In vitro susceptibility testing of the isolates to both the investigational and control drugs. This information should remain blinded while the patient is receiving investigational drug. In vitro susceptibility testing should be performed by using standardized methods.[14]

The investigator should remain blinded to the bacterial isolate and in vitro drug susceptibility testing unless the patient meets the criteria for clinical failure, at which time the results of the bacterial isolate and in vitro susceptibility testing should be made immediately available to the treating clinician.

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

b. On-therapy visits

Each patient should have daily on-therapy assessments of symptoms or observable signs, as well as safety assessments. These assessments can be performed by the investigator during a visit to the investigator's office or by a PRO instrument. Regardless of how the assessment is conducted (e.g., interview, interactive voice response via telephone, PRO), 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 trial outcome. If assessments are done often (e.g., twice daily), the ability to detect differences between therapies for a time-to-resolution endpoint or a fixed time point early in therapy may be increased. Therapy should be continued as described in the protocol regardless of whether symptoms and observable signs have resolved.

Rescue antibacterial drug therapy should be administered to patients who are worsening on their assigned treatment arm; specific criteria to identify these patients should be included in the protocol and the patients should continue to have protocol-specified assessments. 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 later. Although assessments for clinical improvement or clinical failure should be included as part of the on-therapy visits, all patients enrolled in placebo-controlled trials should have a protocol-defined assessment for clinical failure at approximately 48 hours after clinical trial enrollment.

c. Early follow-up visit

The early follow-up visit should occur after completion of investigational drug administration, at a time when the drug is expected to have cleared from the infection site. For example, if an investigational drug with a short half-life is administered for 5 days, this visit can occur on day 7 to 10 after therapy initiation. At this visit the investigator should perform a focused medical history and physical examination, as well as appropriate laboratory measurements. The investigator also should inquire about adverse events.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all investigational drug. For patients with no adverse events noted at the early follow-up assessment and who are clinical successes (i.e., previous resolution of symptoms and signs), 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. Although adverse events that are serious and unexpected are required to be reported and followed until resolution (21 CFR 312.32(c)(1)(i)(A) and 21 CFR 312.32(d)(1) and (2)), we recommend that *all* adverse events be followed to resolution, even if time of trial has been completed.

### *10. Statistical Considerations*

The trial's primary and secondary hypotheses and the analysis methods should be prespecified in the protocol. Sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

#### a. Analysis populations

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

- **Safety population —** All patients who received at least one dose of drug during the trial.
- **Intent-to-treat (ITT) population —** All patients who are randomized.
- **Microbiologically confirmed intent-to-treat (micro-ITT) population —** When tympanocentesis is performed on patients at baseline, this population is all patients who are randomized and who have a pathogen known to cause ABOM isolated at baseline. Patients should not be excluded from this population based upon events that occur after 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 population or micro-ITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of investigational drug).

The ITT population should be evaluated in efficacy analyses as well as the population of patients who follow important aspects of the protocol (i.e., the per-protocol population) to ensure consistency of results. However, it is also 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; because of this, analyses based on the ITT population should be considered the primary analyses, with analyses based on a per-protocol population reviewed for consistency of results.

#### b. 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 noninferiority margin (for a noninferiority trial) or the amount by which the investigational drug is expected to be superior to the control (for a superiority trial).

c. Missing data

There is no optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial by incorporating strategies for adequate follow-up and these strategies should be specified in the protocol. Patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways, posing analytic problems. The way missing data will be handled should be specified in the protocol. Patients who stop trial drug and initiate rescue therapy generally would be counted as nonresponders or failures, but should be followed. Sponsors should prespecify several sensitivity analyses to assess the robustness of the primary analysis, including analyses with multiple imputation methods and classification of all missing outcomes as failures. However, all of these methods depend on uncertain assumptions, and interpretation of trial results may be difficult if there is a high rate of missing data or the rates of missing data are different across treatment arms.

d. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent data monitoring committee (DMC) that monitors the protocol with prespecified operational procedures. Such a committee also might be created if there were safety concerns about the drug or treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, conflicts of interest, decision rules, details on the measures taken to protect operational bias and the integrity of the trial, and standard operating procedures should be provided for review.[15]

e. Other analyses of interest and secondary endpoints

Analyses of secondary and additional endpoints should be considered exploratory because a trial usually is not designed to address the questions raised by these analyses, because of multiple comparisons and/or concerns with subgroup analyses. 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.

[15] For more detailed guidance, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

### *11. Ethical Considerations*

There are concerns that institutional review boards (IRBs) or investigators may consider a placebo-controlled trial in ABOM to be unethical. The general issue of the ethics of placebo-controlled trials is addressed in ICH E10. For such a trial to be approvable by a local IRB under 21 CFR part 50, subpart D, the risk to children randomized to a comparator group that involves the withholding of antibacterial treatment (whether placebo or delayed therapy) must be no more than a minor increase over minimal risk (21 CFR 50.53). In addition, clinical trials must be designed so that risks to patients are minimized (21 CFR 56.111).

Given the specific concern of rare infectious complications that may be associated with nontreatment of ABOM (e.g., mastoiditis or meningitis), the design for a placebo-controlled trial should include an early clinical assessment for clinical failure at approximately 48 hours after enrollment. A review of all previous placebo-controlled trials of ABOM have not shown a substantial risk to placebo-treated recipients that make future placebo-controlled trials unethical; overall 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. If necessary, effective antimicrobial rescue treatment can be initiated at the time of a clinical failure, thus limiting the risk exposure of the children randomized to the placebo-controlled arm of the trial.

If tympanocentesis is included in the trial design, it should be performed only by individuals with expertise in this procedure to ensure that the procedure poses no more than a minor increase over minimal risk to patients (21 CFR 50.53). Making unblinded culture results available so that effective antimicrobial treatment can be initiated in response to a treatment failure may provide prospect of direct benefit to the enrolled children, and thus be acceptable under 21 CFR 50.52. In addition, targeted therapy based on culture results from repeat tympanocentesis performed to assess clinical failures may offer prospect of direct benefit.

Finally, for an isolated single-dose PK trial in children, sufficient evidence of drug safety in adults would be needed so that the risk exposure for children is limited to no more than a minor increase over minimal risk (21 CFR 50.53). If the PK data are used to adjust the dose of the investigational drug for individual patients, an IRB may consider this aspect of the trial as offering the prospect of direct benefit (21 CFR 50.52). If additional PK data are collected in an efficacy trial, the PK component of the efficacy trial may be acceptable as a minor increase over minimal risk, based on a component analysis of risk (21 CFR 50.53).

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