Guidance for Industry

Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

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

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TABLE OF CONTENTS

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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 antimicrobial drugs[2] for the treatment of acute bacterial exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD), a disease that previously has been referred to as acute bacterial exacerbations of chronic bronchitis (ABECB). (The term ABECB-COPD is further defined in section III.A.2., Definition of ABECB-COPD.)

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

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 treatment of ABECB-COPD. It does not address issues related to the development of drugs for COPD or COPD exacerbations caused by factors other than bacterial

[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.

infection, and does not address issues related to the development of drugs for the prevention of ABECB-COPD. Information regarding developing drugs for the treatment of COPD is available in the draft guidance for industry *Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment*.[4]

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

II. BACKGROUND

Since the FDA published its first draft guidance on the development of antimicrobial drugs for the treatment of ABECB in 1998, there have been several public discussions regarding the design of clinical trials to study indications for infections involving the respiratory tract, including the indication of ABECB-COPD.[5] These discussions have focused on trial design issues for ABECB-COPD such as the following:

- Superiority versus noninferiority trial designs
- Use of a placebo control
- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of efficacy outcome measures
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes

Since these public discussions were held, publications of reviews and treatment guidelines of ABECB-COPD have suggested a stratified approach in which antibacterial drugs are recommended for patients with ABECB-COPD characterized as *moderate* or *severe*, but not for patients with ABECB-COPD characterized as *mild*. This guidance discusses the trial design issues listed above as well as a different stratification for ABECB-COPD based on *inpatient* versus *outpatient* treatment (see Appendix A).

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

[5] The design of ABECB clinical trials was discussed at a meeting of the Anti-Infective Drugs Advisory Committee on February 19, 2002, and an Infectious Diseases Society of America/Pharmaceutical Research and Manufacturers of America/FDA workshop on November 19-20, 2002. Transcripts of these meetings are available at http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3837t1.htm and http://www.regulations.gov/#!documentDetail;D=FDA-2002-N-0319-0003, respectively.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

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

2. Definition of ABECB-COPD

The term ABECB-COPD is used in this guidance to more accurately identify the disease that has previously been referred to as acute bacterial exacerbations of chronic bronchitis. ABECB-COPD refers to a clinical diagnosis of presumptive bacterial infection superimposed on a chronic pulmonary condition. This situation is best described pathologically as bronchial inflammation associated with the isolation of pathogenic bacteria from sputum or bronchial lavage specimens. However, it is important to note that there is some uncertainty as to the role of bacteria in causing ABECB-COPD because chronic bacterial colonization may be present in the airways of patients with COPD.

The acute component of ABECB-COPD is usually manifested as a worsening of the same symptoms patients experience when they are not experiencing an acute infection.[6] Accordingly, to enroll patients in ABECB-COPD trials, clinical trials should be designed to:

- Define and document the underlying pulmonary condition in enrolled patients
- Accurately measure the symptoms of the acute episode at trial entry
- Define the criteria for occurrence of an episode of ABECB-COPD (i.e., the change in symptoms that define an acute episode against the background of chronic pulmonary disease)

3. Efficacy Considerations

FDA review of previous ABECB-COPD trials has not been able to establish a reliable estimate of the magnitude of benefit for antibacterial drug treatment of ABECB-COPD, which is a precondition for a noninferiority trial.[7] Accordingly, only superiority trials are currently recommended for ABECB-COPD.[8]

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[6] See References, section D., Publications that provide definitions for COPD and ABECB-COPD.

[7] See ICH E10 and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

[8] We recognize that treatment guidelines suggest a stratification of patients in which those with more severe ABECB-COPD should receive treatment with an antibacterial drug. A reliable and well-defined magnitude of the treatment effect for patients with more severe ABECB-COPD has not been established.

The goal of ABECB-COPD clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABECB-COPD associated with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*. If sponsors wish to add additional organisms to this indication based on current epidemiological data or other organisms encountered in the clinical development, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in ABECB-COPD. Bacteria that may be colonizers following recent antimicrobial therapy are unlikely to be pathogens in this setting.

The number of trials that should be conducted in support of an ABECB-COPD indication depends on the overall development plan for the drug under consideration. If the development plan for a drug has ABECB-COPD as the sole marketed indication, then two adequate and well-controlled trials establishing safety and efficacy should be conducted.

A single randomized, double-blind trial supporting the indication may be appropriate if data demonstrate effectiveness in other lower respiratory tract diseases. For example, robust findings of efficacy from well-designed community-acquired bacterial pneumonia development programs with similar dosing regimens may be supportive of a single superiority trial of ABECB-COPD.

The disease course and treatment for ABECB-COPD 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 ABECB-COPD trials. Sponsors who wish to propose use of a surrogate marker should discuss this with the FDA early in the drug development process.

4. Safety Considerations

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 includes the ability to evaluate the potential for relatively uncommon serious adverse events as well as commonly expected adverse events. The information should be derived primarily from adequate and well-controlled trials of ABECB-COPD, but also can be derived from trials of the new drug for infections other than ABECB-COPD if exposure is similar to or greater than the exposure for ABECB-COPD. The total number of patients needed for a drug development program that includes an ABECB-COPD indication should be discussed with the FDA early in the drug development process.

Antimicrobials with clinically significant toxicity may not be appropriate for study of ABECB-COPD unless the treatment goal is directed at a more seriously ill patient portion of the ABECB-COPD population.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Design

As previously mentioned, we recommend only superiority trials for ABECB-COPD trials (see section III.B.11.b., Noninferiority margins).

Superiority trials in the treatment of ABECB-COPD can consist of the following forms:

- **Placebo-controlled trial with a background of best available nonantimicrobial therapy —** All patients receive the best available nonantimicrobial therapy and are randomized to receive, in addition, an investigational antibacterial drug or matching placebo. To demonstrate efficacy, the group receiving the investigational antibacterial drug should demonstrate superiority to the control group receiving matching placebo. A three-arm trial with the experimental treatment group, an active comparator group, and a placebo-controlled group permits the demonstration of superiority to placebo and also can provide risk-benefit information relative to an approved comparator.

- **Dose-response —** Patients in each treatment group receive different doses (or dosing regimens) of an investigational antibacterial drug together with the best available nonantimicrobial therapy. To demonstrate efficacy, the group receiving a higher dose (or more intensive therapy) should be superior to the lower dose (or less intensive) regimen.

- **Superiority of the trial antimicrobial to another antimicrobial —** Patients in one group receiving the investigational drug (with best available background nonantimicrobial therapy) are compared with patients in a control group receiving another antibacterial drug (with best available background nonantimicrobial therapy). To demonstrate efficacy, the group receiving the investigational antibacterial drug should demonstrate superiority to the group receiving the control antibacterial drug.

ABECB-COPD trials should be parallel group designs because crossover designs may be subject to carryover and period effects. Other trial designs to demonstrate superiority can be discussed with the FDA.

2. Trial Population

ABECB-COPD clinical trials should enroll males and females 35 years old and older because COPD occurs primarily in older individuals; a diagnosis in younger individuals may reflect misclassification. We anticipate that most patients in ABECB-COPD clinical trials will be older than 50 years of age. ABECB-COPD does not occur in a pediatric population.

We recognize that it is not appropriate for patients with ABECB-COPD of greater severity (e.g., patients who are mechanically ventilated) to be enrolled in placebo-controlled trials of a new antibacterial for ABECB-COPD. We strongly encourage discussion with the review division if study of patients with greater severity is being considered. It is essential that in any proposed trials, adequate provisions are in place so that human subjects are not exposed to an unreasonable and significant risk of illness or injury (21 CFR 312.42).

3. Entry Criteria

The diagnosis of ABECB-COPD can be challenging. Both a diagnosis of COPD and an acute change superimposed against the background of chronic symptoms should be used for trial enrollment.

Traditionally, COPD has been defined as containing aspects of chronic bronchitis and emphysema. A diagnosis of chronic bronchitis is made clinically based on the presence of symptoms of cough and sputum production on most days of 3 consecutive months in at least 2 consecutive years. Although useful for clinical practice, this definition lacks specificity for clinical trials because there is no standardized definition of the number of days that constitutes *most* days of 3 months out of the year or quantification of degree of sputum and cough.

Because of the overlap of symptoms in patients with chronic bronchitis and/or emphysema and the limitations of the definition of chronic bronchitis, it is more appropriate to use the term COPD to describe the underlying disease in this patient population. The definition and severity of underlying obstructive pulmonary disease is based on the results from spirometry testing compared to predicted normative values as follows:

- Mild COPD = FEV1/FVC < 70% and FEV1 ≥ 80% predicted
- Moderate COPD = FEV1/FVC < 70% and 50% ≤ FEV1 < 80%
- Severe COPD = FEV1/FVC < 70% and 30% ≤ FEV1 < 50%
- Very severe COPD = FEV1/FVC < 70%, or FEV1 < 30% predicted or FEV1 < 50% plus chronic respiratory failure

Spirometry may be difficult to perform at the time of ABECB because these tests are effort dependent. Spirometry data used for enrollment should be obtained from recent medical records; patients without spirometry-documented COPD should not be enrolled in ABECB-COPD trials. Spirometry data obtained at the time an episode of ABECB-COPD is diagnosed have not been demonstrated to be predictive of severity or outcome.

The diagnosis of an acute exacerbation presents additional concerns. A diagnosis of ABECB-COPD reflects a change in patient symptoms from their usual baseline; for a trial to demonstrate efficacy of antimicrobial therapy to be effective, patients who have a true change in symptoms should be selected. Because symptoms and signs as reported by the patient are critical to the diagnosis and clinical management of COPD and ABECB-COPD, a well-defined and reliable patient-reported outcome (PRO) instrument should be used in clinical trials for the treatment of ABECB-COPD.[9]

The specificity of sputum cultures for selecting patients with bacterial disease is unknown in ABECB-COPD because sputum is not normally sterile between exacerbations in these patients, and the etiologic role of bacteria in ABECB-COPD is uncertain. However, if there is a pathogenic role for bacteria in this disease, a negative sputum culture may reduce the chance of demonstrating a significant benefit from an antibacterial drug. Sponsors may wish to restrict

[9] Sponsors should define the description of ABECB-COPD to be used in the inclusion criteria. We are also aware of ongoing evaluations of a PRO instrument in ABECB-COPD.

enrollment in trials to patients with a positive sputum culture at baseline for any one of the three most common bacteria implicated as a cause of ABECB-COPD (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).[10]

a. Inclusion criteria

The following are recommended inclusion criteria for patient enrollment in trials conducted for the treatment of ABECB-COPD.

- **Patient history and characteristics.** The following patient demographic characteristics should be used for a better chance of selecting patients more likely to have ABECB-COPD:

  - Male and female patients 35 years old and older
  - History of at least mild COPD previously defined by the spirometry criteria above
  - History of more than two previous episodes of acute exacerbations in the previous year
  - History of tobacco use consistent with a diagnosis of COPD

- **Signs and symptoms.** Signs and symptoms that can be present in patients over the previous 7 days with ABECB-COPD include the following:

  - Increased dyspnea or breathlessness
  - New or increased cough
  - New or worsening chest tightness or discomfort
  - Sleep disturbances (i.e., insomnia or sleepiness)
  - Decrease in exercise tolerance or limitation of usual activities
  - Increase in sputum volume and/or sputum purulence
  - New or increase in wheezing
  - New or worsening crackles on auscultation of lung fields

  Generalized signs and symptoms occurring over the previous 7 days that are consistent with a diagnosis of ABECB-COPD (but are otherwise nonspecific) include:

  - Fever (e.g., temperature greater than 38.0 degrees Centigrade)
  - Malaise or fatigue
  - Confusion or change in mental status

[10] This situation can be addressed by use of a run-in period, if feasible, when patients with a negative culture at baseline are excluded before beginning trial therapy or during analysis by analyzing patients with a positive culture at baseline separately. This is discussed further in sections III.B.10., Clinical Trial Visits and Timing of Assessments, and III.B.11., Statistical Considerations.

All signs and symptoms that may be present in patients with ABECB-COPD should be captured on the case report form (symptoms and patient-reported signs should be captured by a PRO instrument), as should current tobacco use.

b. Exclusion criteria

The following patients should be excluded from trials for the treatment of ABECB-COPD:

- Patients with ABECB-COPD characterized as severe (e.g., requiring hospitalization).
- Patients with pneumonia documented by chest X-ray at the time of initial screening. All patients should receive a screening chest X-ray before or at enrollment.
- Patients with asthma and no evidence of other chronic lung disease.
- Patients with any concomitant illness that may confound the interpretation of the effect of trial drugs (e.g., pulmonary malignancy, congestive heart failure, bronchiectasis, pneumothorax).
- Immunocompromised patients; however, patients receiving systemic corticosteroids at baseline for treatment of COPD can be enrolled.
- Patients who are allergic to any of the trial drugs.

Depending on the trial design, sponsors also may wish to exclude patients who have received antimicrobial therapy for the current episode of ABECB-COPD, or alternatively, permit enrollment of patients with symptoms that are not improving or worsening on prior antimicrobial therapy.

4. Randomization, Stratification, and Blinding

Patients should be randomized for receipt of trial drugs at enrollment. If trials allow enrollment of patients who have received prior antimicrobial therapy, prior antibacterial drug therapy should be included as a stratification factor. All trials should be double-blinded.

5. Special Populations

Drug development programs should include a sufficient number of geriatric patients, including patients older than 75, to characterize safety and efficacy in this population.[11] Pharmacokinetics of the drug in patients with hepatic impairment or in patients with renal impairment may be evaluated before initiation of phase 3 trials to determine whether dose adjustments are necessary; this evaluation may help avoid the exclusion of such patients from phase 3 clinical trials.

[11] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

6. Dose Selection

Data from phase 1 and phase 2 studies and dose-ranging pharmacokinetic/pharmacodynamic studies (including information regarding bronchial/lung penetration of the drug) can be integral to selecting an appropriate dose and duration of therapy for phase 3 clinical trials.

7. Choice of Comparators

The control group for these superiority trials can be placebo or another antibacterial drug.

8. Concomitant Medications

Patients can receive appropriate nonantimicrobial therapies at the time of enrollment based on their condition, which may include bronchodilator and/or systemic corticosteroid 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 therapy 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.

Because nonantimicrobial therapies might influence a PRO instrument scale, it is emphasized that treatment groups should be balanced in the use of nonantimicrobial therapies to minimize confounding and ensure that a treatment effect on a PRO outcome measure would be attributed to the investigational antibacterial drug over the control (e.g., placebo). 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 (e.g., bronchodilator treatment, or protocol-specified rules for the addition of nonantimicrobial therapy such as corticosteroids). At a minimum, the protocol should specify appropriate options for nonantimicrobial therapies during the trial.

We anticipate that changes in the use of the following medications will be monitored or specified in an ABECB-COPD trial and should be balanced between treatment groups:

- Changes in the frequency or dose of beta-agonist therapy, or the addition of new beta-agonist therapy (long- or short-acting therapy)

- Changes in the frequency or dose of anticholinergic therapy or the addition of an anticholinergic therapy

- Addition of methylxanthine therapy

- Changes or the addition of systemic corticosteroids; systemic corticosteroids should be administered in a standardized way in the trial (e.g., to all patients with a pre-enrollment FEV1 of < 50% of predicted FEV1)

Assessment of the need for concomitant medications as an endpoint may not be reflective of the persistence of patient signs or symptoms; the presence of such signs or symptoms should be confirmed by a PRO instrument that shows continued signs or symptoms at the time of administration of the concomitant medication.

9. Efficacy Endpoints

a. Evaluation of clinical response

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 method of assessing patient symptoms should be used for ABECB-COPD trials. Accordingly, we recommend use of a valid and reliable PRO instrument as the primary outcome measure.[12] The same PRO instrument also should be used at baseline to define enrollment criteria; the severity level based on the PRO instrument's score should be sufficient to allow observation of a clinically meaningful response (i.e., change on the PRO instrument). The direction and magnitude of change, improvement or worsening, determined to be clinically meaningful (and therefore appropriate for regulatory decisions) should be determined during instrument development and should be discussed with the FDA before trial initiation. Statistically significant differences between comparator regimens may not be sufficient for demonstrating treatment benefit in terms of how a patient feels or functions if response to treatment has not been confirmed to be clinically meaningful to patients. For example, signs or symptoms used to diagnose ABECB-COPD that may be important to a clinician, such as the color of sputum, may not be an important outcome to patients and therefore would not be appropriate as part of the score used in the efficacy endpoint to determine response to treatment.

If an adequate PRO instrument for ABECB-COPD is available for studying ABECB-COPD, it should be incorporated in the entire clinical development program. The use of a PRO instrument in phase 2 trials of patients with ABECB-COPD can provide additional data about clinical activity and can inform the design and use of the PRO instrument in phase 3 clinical development plans (e.g., sample size calculations). If an adequate instrument for studying ABECB-COPD is not available at the outset of the clinical development program, we recommend that the new instrument development process begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.

Patients with ABECB-COPD are unlikely to be asymptomatic at the end of trial treatment, and may not even return to their baseline status before the onset of the acute episode. Improvement

[12] The use of a well-defined and reliable PRO instrument can yield greater assurance that symptoms are being measured in a consistent manner across patients. 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*.

of symptoms over time as measured by a well-defined and reliable PRO measure should be the primary efficacy endpoint rather than return to previous baseline.

A fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-improvement analysis. For example, clinical outcome at greater than 3 weeks after onset of therapy may not show a difference between treatment arms because many patients may have resolution of the acute exacerbation by this time, regardless of the administration of antibacterial drug therapy. 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.

An outcome scale can be used for describing categorical responses (e.g., *improvement* or *failure*) at each time point if the criteria for the categories are well-defined and reliable. Overall response should also incorporate survival and the absence of complications of ABECB-COPD as part of the overall response assessment (e.g., the development of pneumonia should be considered a clinical failure). Failure criteria should be defined a priori (e.g., protocol-defined worsening of symptoms, failure to improve at certain time points after treatment onset). Failure should likely mandate a change in treatment, which should include *active* therapy for the placebo arm.

Other measures such as pulmonary function testing or exercise testing (e.g., a *6-minute walk*) can be incorporated into a clinical protocol and should be considered secondary outcome measures.

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

Early clinical assessment for treatment failure should be performed in a placebo-controlled trial so that *rescue* therapy can be incorporated into the trial design at the time a failure outcome is assigned; this process can serve to mitigate concerns regarding inclusion of a placebo arm in an ABECB-COPD trial.

b. Clinical relapse or recurrence

Patients who initially improve and then experience worsening of signs and symptoms of ABECB-COPD during the trial should be considered as treatment failures because of relapse or recurrence of ABECB-COPD. These patients should be re-evaluated clinically and microbiologically to distinguish between clinical relapse (with persistence of the same bacterial pathogen) and clinical recurrence (infection with a new bacterial pathogen). This distinction may be useful for trials that examine clinical recurrence as a secondary endpoint (i.e., assessment of the prolonged effect from antibacterial treatment of a single episode). Patients who continue to demonstrate clinical improvement during the trial, yet do not return to their baseline COPD status before ABECB-COPD, should not be characterized as clinical relapse or recurrence.

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 trial drug therapy. These patients should not be necessarily considered

withdrawn from the trial in terms of overall evaluation; investigators should continue to follow all such patients at scheduled visits and continue to record information on both safety and efficacy outcomes. If at the time 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. If a trial patient maintains clinical improvement of ABECB-COPD after discontinuation of therapy because of an adverse event, the patient should not be automatically considered a clinical failure.

Patients who receive another antibacterial drug while on trial drug therapy should be identified because these patients should be considered failures in an efficacy analysis.

d. Microbiological response

Although microbiological outcome may provide useful information regarding the biological activity of antimicrobials, microbiological outcome is not a direct measure of benefit to patients. Microbiological outcome should be viewed as being supportive information, but not as a substitute for clinical outcome in a specific trial.[13]

If follow-up specimens for culture are obtained from patients, the most useful specimens are those obtained at least 72 hours after the completion of drug therapy because negative culture results obtained while on therapy may represent suppression rather than elimination of organisms. Any target pathogens isolated from follow-up specimens should be tested for susceptibility to the antimicrobial used to treat the disease.

All target pathogens isolated from patients during clinical trials should be appropriately saved in the event that there is a need to do additional trials with the bacteria.

10. Clinical 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. The following information should be recorded on the case report form during the entry examination.

- **History and demographic characteristics**

  - Date of visit.
  - Age, sex, and weight.
  - Underlying medical condition(s).
  - Current medications.

[13] Microbiological outcomes may be valuable in phase 2 trials addressing dosing regimens (i.e., where time to no growth on culture is being used as an outcome to optimize dose and/or dosing frequency).

- Number of distinct and well-documented episodes of acute bronchitis in the past, including how this information is obtained (i.e., chart review or patient recall); dates, treatment regimens, and outcomes should be recorded.

- Detailed history of COPD including results of prior pulmonary function testing. This history is best obtained from objective sources (e.g., patient medical records).

- History of tobacco use.

- Recent or current use of antibacterial drugs, and the indication or reason for use.

- Bacteria previously isolated from sputum during previous exacerbations, with antimicrobial susceptibility profile.

- **Symptoms**

  A well-defined and reliable PRO instrument, as discussed in section III.B.9., Efficacy Endpoints, should be used to assess symptoms at baseline.

- **Signs**

  - Vital signs, including body temperature measurement

  - Posteroanterior and lateral chest X-rays[14]

  - Electrocardiography (to rule out arrhythmia and for safety analysis)

  - Other laboratory tests for evaluation of safety parameters (e.g., complete blood count, serum chemistries)

- **Sputum sample collection**

  The entry visit should include baseline sputum Gram stain with submission of sputum for culture and susceptibility testing. Sponsors should describe in the protocol the methods of obtaining specimens, specimen processing, and culture techniques. For microbiological assessment, the investigator should collect the following information:

  - A description of how the sample was obtained (e.g., expectoration, induced sputum, aspiration), processed, and transported to the laboratory.

[14] Patients should have a baseline chest X-ray to rule out pneumonia and other confounding illnesses such as congestive heart failure, malignancy, or bronchiectasis. Spiral computed tomography and D-dimer testing can be indicated in selected patients to exclude pulmonary embolism.

- The adequacy of the specimen in terms of numbers of polymorphonuclear cells and epithelial cells present.[15]

- Identification of bacterial isolates.

- In vitro susceptibility (preferably minimum inhibitory concentration) testing of the isolates to both the trial and control drugs. In vitro susceptibility testing should be performed by using standardized methods, such as the Clinical and Laboratory Standards Institute methods, unless otherwise justified.

Microbiological information that is not part of the entry criteria (e.g., susceptibility results) should remain blinded to investigators. Previous trials have shown that patients with the following characteristics may be more likely to have bacteria isolated by sputum culture at baseline:

- Purulent sputum
- Patients with more than two episodes of acute bronchitis per year
- Patients with a positive baseline sputum Gram stain

Clinical outcome results should be evaluated by sputum culture data for each pathogen (e.g., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).

b. On-therapy visits

Each patient should have daily on-therapy assessments of signs and symptoms using a well-defined and reliable PRO instrument. Regardless of how the assessment is conducted (e.g., using an interviewer-administered PRO, interactive voice response via telephone, or electronic capture using a mobile device), the questioning of patients should be performed in a valid, reproducible, and structured way to minimize the potential for inconsistencies in the assessment.[16] The ability to detect differences between therapies for a time-to-improvement 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 improved. Investigators should attempt to allow a minimum of 72 hours on therapy with the trial drug therapy before classifying a patient as a clinical failure; accordingly, investigators may wish to include a 48- to 72-hour visit to ensure there is no substantial clinical worsening at this time.

Assigning an outcome of clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening on their assigned treatment; specific criteria to identify these patients should be included in the protocol. It is important that investigators

[15] Investigators should evaluate the adequacy of sputum samples by ensuring that the specimen is most likely from lower respiratory secretions by use of the following factors: greater than 25 white blood cells per field at 100x magnification (low power, 10x objective) confirming the impression of *sputum purulence* and fewer than 10 squamous epithelial cells at 100x magnification (low power, 10x objective).

[16] When interviews are used they should be standardized; in addition, symptoms recorded from the patient should be recorded without interpretation by the interviewer. See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

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. The protocol should also specify a failure endpoint if symptoms have not improved by a certain day, even if the symptoms are not clinically worsening at that time; this may be most objective if defined as a score remaining above a certain threshold for a PRO instrument. In general, patients should not be unblinded if a criterion for rescue therapy is met.

In the case of clinical failure, therapy should be changed to include initiation of antibacterial therapy and/or other appropriate therapeutic modifications as necessary. Protocols should define the choice of the antibacterial therapy to be used in the case of clinical failure. If failure is assigned, the investigator should attempt to obtain a repeat sputum culture and the sample should be sent for culture and susceptibility testing. Patients who meet criteria for clinical failure should continue to have the identical protocol-specified assessments as patients who continue to receive their originally assigned treatment.

Investigators should document findings from on-therapy office visits on the case report form (e.g., history, physical examination, and laboratory test results). 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 well-defined and reliable diary is used to capture patient symptoms during this visit, this information also should be recorded on the case report form.

Consideration should be given to obtaining blood samples 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 drug is expected to be clear from the infection site (usually at least 5 half-lives). For example, if a drug with a short half-life is administered for 10 days, this visit can occur at completion of trial drug therapy or up to 4 days after completion of therapy; this visit should occur later for drugs with a longer half-life. 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. Depending on the trial design, follow-up sputum culture may be appropriate at this visit.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all trial drug therapy (e.g., if trial drug is administered for 10 days, this assessment can occur on days 20 to 25 after therapy initiation (unless a drug with a long half-life has been studied)). 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.

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 (e.g., additional electrocardiogram measurements). Longer-term assessment of adverse events after discontinuation or completion of the antibacterial drug therapy 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.[17] All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

11. Statistical Considerations

Sponsors should designate the hypotheses to be tested before trial initiation. These hypotheses should be stated in the protocol or statistical analysis plan, and the trial should be powered to detect differences between treatment arms if group differences exist. 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 specify the order of hypothesis testing before trial initiation and the method for controlling the overall type I error rate. These issues should be discussed with the FDA in advance of trial enrollment, and should be incorporated into the statistical analysis plan as appropriate.

a. Analysis populations

The following definitions apply to various populations for analyses in ABECB-COPD 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 —** All patients who are randomized and who have a pathogen associated with ABECB-COPD isolated at

[17] For specific safety reporting recommendations during clinical trials, see the ICH guidance for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

baseline. Patients should not be excluded from this population based upon events that are measured 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 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 diary, urine testing, or MEMS caps).

To ensure consistency of results, the ITT and/or micro-ITT populations should be evaluated as well as the population of patients who follow important aspects of the protocol (i.e., the per-protocol populations). 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 (or micro-ITT) population should be considered the primary analyses, with analyses based on a per-protocol population reviewed for consistency of results. Results in both populations should provide evidence of effectiveness.

The primary and secondary analyses should be defined in the protocol before trial initiation. Depending on the exact hypothesis being tested, sponsors may prefer to specify either the ITT or micro-ITT population as the primary population for analysis. For example, because an effect of an antibacterial drug is most likely to be seen in patients with *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* or other likely bacterial pathogens isolated at baseline, the trial can be powered for the micro-ITT population and this should be the primary analysis population. If it is expected that the investigational drug arm will be superior to the placebo arm for all patients enrolled, even patients who did not have a pathogen isolated, then an ITT population would be the most appropriate primary analysis population. The choice of population (i.e., micro-ITT or ITT) for the primary analysis may guide the details of product labeling if the drug is approved.

b. Noninferiority margins

As previously mentioned, FDA review of previous ABECB-COPD trials has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD with antibacterial drug therapy. Because of this, we do not recommend using noninferiority trials to establish evidence of effectiveness for regulatory approval of a new indication for ABECB-COPD. Sponsors who are considering a noninferiority trial for ABECB-COPD should justify to the FDA the proposed noninferiority margin by data that include reliable estimates of a well-defined efficacy outcome measure. Such justification should be discussed with the FDA as early as possible during protocol development and before trial initiation. For additional information regarding noninferiority trials in general and in antibacterial trials, see ICH E10, the guidance for

industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*, and the draft guidance for industry *Non-Inferiority Clinical Trials*.[18]

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 noninferiority margin (for a noninferiority trial), or the amount by which the trial drug is expected to be superior to the control (in a superiority trial). Sample size should be based upon the number of patients needed to draw conclusions in the ITT or micro-ITT analysis population.

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 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 addressed 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 occurs, it should be addressed in the final report.

e. Interim analyses and data monitoring committee

If interim (or futility) analyses will be performed, they should be specified in the analysis plan. The purpose of the interim analysis should be stated in the analysis; it is important that the interim analysis not affect trial conduct and thereby compromise trial results. Trial 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 trial initiation to ensure that the overall trial significance tests properly address the effect of interim testing.

Use of a data monitoring committee (DMC) may be appropriate depending on the design of the proposed phase 3 trial and the patient population that the trial will enroll. If a DMC is used, a detailed charter with the composition of the committee members and the operational details should be provided for review.[19]

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

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

f. 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, either 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.

g. Statistical analysis plan

Before initiation of any phase 3 trial, sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

12. Ethical Considerations

Review of previous placebo-controlled trials involving the treatment of ABECB-COPD has shown variable results, with several placebo-controlled trials showing no effect for antimicrobial treatment of exacerbations. Accordingly, for patients with ABECB-COPD of lesser severity, 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 addition may serve to mitigate concerns regarding inclusion of a placebo group in an ABECB-COPD trial. All trial designs should provide appropriate provisions for patient safety.

Although results have been varied, some previous ABECB-COPD trials have shown clinically significant benefit in patients with a greater severity of illness (e.g., patients with ABECB-COPD receiving mechanical ventilation). We strongly encourage discussion with the FDA regarding trial design if enrollment will include patients with clinically severe disease (e.g., patients requiring hospitalization or at immediate risk of respiratory failure).

C. Other Considerations

1. Animal Models

There are no animal models for ABECB-COPD. However, animal models for other upper and lower bacterial infections by the same microorganisms implicated as a cause of ABECB-COPD may be useful in determining antimicrobial candidates for further study in the treatment of ABECB-COPD.

2. Labeling Considerations

The following is an example of a labeled indication for the treatment of ABECB-COPD:

> *"[Drug] is indicated in the treatment of acute exacerbations of chronic bronchitis in patients with underlying chronic obstructive pulmonary disease (ABECB-COPD) due to susceptible isolates of [relevant pathogens based on trial results]."*

The labeling should describe the disease severity of patients enrolled in the clinical trials.

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

APPENDIX A: STRATIFIED APPROACH FOR CHARACTERIZING PATIENTS WITH ABECB-COPD IN PLACEBO-CONTROLLED TRIALS

In general, patients with greater severity of ABECB-COPD (i.e., *moderately ill* or *severely ill*) should be offered treatment with an antibacterial drug.[21] Two publications that are addressed in reviews and treatment guidelines showed that antibacterial drug therapy among patients hospitalized for treatment of ABECB-COPD was associated with a decrease in mortality. One of these publications described the results of a placebo-controlled trial in patients who received mechanical ventilation in an intensive care unit for their ABECB-COPD; in this trial, patients randomized to receive an antibacterial drug had a lower mortality rate. The other publication evaluated retrospective data among patients hospitalized for ABECB-COPD and found an association between the use of antibacterial drugs before hospitalization and a lower mortality rate.[22]

Thus, patients who are hospitalized for ABECB-COPD (a population generally considered to have greater severity of ABECB-COPD) should not be enrolled in trials designed with a placebo control; this recommendation is consistent with the public discussions that occurred in 2002.[23]

The reviews and treatment guidelines do not recommend antibacterial drug therapy for patients with mild ABECB-COPD. We evaluated the published placebo-controlled trials that enrolled patients with ABECB-COPD who were managed as outpatients to determine whether there may be an identifiable treatment difference between antibacterial drug therapy and placebo in patients with mild ABECB-COPD.

We identified eight placebo-controlled trials that enrolled outpatients with ABECB-COPD.[24] Among these trials, three used the following outcome measures that did not incorporate information about patient symptoms: (1) mean duration of ABECB-COPD; (2) assessments of observed clinical signs; and (3) pulmonary function testing. None of these three trials demonstrated a difference between antibacterial drugs and placebo with the use of these different outcome measures.

Among the five trials in outpatients that used an outcome measure incorporating patient symptoms, four showed a statistically significant treatment difference from placebo. In addition, one trial evaluated a symptom-based outcome measure earlier in therapy (i.e., at day 5), and showed a treatment difference that was larger than symptom-based outcome measures evaluated at the end of therapy or after therapy had been completed. The results of this trial suggest that outcome measures based on symptom improvement earlier in therapy may be more sensitive predictors of significant differences between investigational therapy and placebo.

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[21] See References, section A., Treatment guidelines and reviews of ABECB-COPD.

[22] See References, section B., Clinical trials evaluating hospitalized patients with ABECB-COPD.

[23] See http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3837t1.htm and http://www.regulations.gov/#!documentDetail;D=FDA-2002-N-0319-0003.

[24] See References, section C., Placebo-controlled trials enrolling outpatients with ABECB-COPD.

The types of symptom evaluations incorporated into the outcome measures in these trials were different, and it was not possible to describe a reliable treatment effect based on any particular symptom improvement or scoring system. Among patients randomized to receive placebo, there were no reports of serious infectious complications, and there was a trend toward fewer adverse event reports.

A review of these data demonstrates that patients with ABECB-COPD of lesser severity can be appropriately managed through outpatient care, and can be enrolled in trials designed with a placebo control (see also section III.B.12., Ethical Considerations). A superiority finding of an effective antibacterial drug over placebo may be more likely when the symptom improvement outcome measure is evaluated earlier in therapy, instead of at the end of therapy or at a period of time after completion of therapy.