Guidance for Industry

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

DRAFT GUIDANCE

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

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

August 2008
Clinical Antimicrobial
Revision 1

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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of antimicrobial drugs for the treatment of acute bacterial exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and designs of clinical trials for antimicrobial drug products to support an indication for treatment of ABECB-COPD.[2] This guidance does not address issues related to the development of drugs for other purposes such as prevention of respiratory tract infections in patients with COPD or in other populations, such as otherwise healthy persons. We expect that this guidance will serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products, the Division of Special Pathogen and Transplant Products, and pharmaceutical sponsors, the academic community, and the public.[3] Since the science of this indication continues to evolve, this guidance may be revised as new information becomes available.

This guidance revises the draft guidance for industry *Acute Bacterial Exacerbation of Chronic Bronchitis — Developing Antimicrobial Drugs for Treatment* published in 1998. It also

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

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

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

supersedes, with regard to the development of drugs to treat ABECB-COPD, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective drugs (Systemic*) and *Clinical Development and Labeling of Anti-Infective Drug Products*,[4] as well as the joint FDA/Infectious Disease Society of America's *Guidelines for the Evaluation of Anti-Infective Drug Products*).[5]

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials*, *E9 Statistical Principles for Clinical Trials*, and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[6] This guidance focuses on specific drug development and trial design issues that are unique to the study of ABECB-COPD; it does not address issues regarding the development of drugs for COPD or COPD exacerbations caused by factors other than bacterial infection. 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.*[7]

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 draft guidance on the development of antimicrobial drugs for the treatment of ABECB in 1998, there have been public discussions regarding the design of clinical trials to study indications for infections involving the respiratory tract, including the indication of ABECB-COPD.[8] These discussions have focused on the appropriateness of noninferiority trial designs for ABECB-COPD and other important study design issues such as the following:

[4] See the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

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

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

[8] The design of ABECB clinical trials was discussed at a meeting of the Anti-Infective Drugs Advisory Committee on February 19, 2002, and an IDSA/PhRMA/FDA workshop on November 19-20, 2002. Transcripts of these meetings are available at http://www.fda.gov/cder/audiences/acspage/antiinfectivemeetings1.htm and http://www.fda.gov/cder/present/idsaphrma/default.htm, respectively.

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

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

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New drugs being studied for ABECB-COPD should have preclinical data documenting activity against the pathogens most commonly associated with ABECB-COPD (i.e., *S. pneumoniae*, *H. influenzae*, and *M. 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 manifest as worsening of the same symptoms patients experience when they are not experiencing an acute infection. Accordingly, to enroll patients in studies of ABECB-COPD, 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 study 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 studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD by antimicrobials (a precondition for

a noninferiority trial).[9] Accordingly, only superiority trials are currently recommended for ABECB-COPD studies.

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

The number of studies 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 at least two adequate and well-controlled trials establishing safety and efficacy should be conducted.

A single randomized, double-blind study supporting the indication may be appropriate if the sponsor has access to confirmatory evidence including data from other clinical studies demonstrating effectiveness in other lower respiratory tract diseases and there is additional supportive information such as pharmacokinetic (PK) and pharmacodynamic (PD) studies demonstrating concentration of the antibacterial drug in the bronchi at a level expected to be active against the common pathogens causing ABECB-COPD. For example, robust findings of efficacy from well-designed community-acquired pneumonia trials with similar dosing regimens may be supportive of a single superiority trial of ABECB-COPD.

Currently, there are no surrogate markers accepted by the FDA as substituting for clinical outcomes in ABECB-COPD studies. 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 studies of ABECB-COPD, but also can be derived from studies 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.

[9] See ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

B. Specific Efficacy Trial Considerations

1. Study Design

As previously mentioned, we recommend only superiority trials for ABECB-COPD studies.[10] Superiority trials in the treatment of ABECB-COPD can consist of the following forms:

- **Placebo-controlled study with a background of *optimized* nonantimicrobial therapy —** Patients in one study arm receive an experimental drug added to a standardized nonantimicrobial regimen. To demonstrate efficacy, the arm receiving the test antimicrobial should demonstrate superiority to a control arm of the same standardized nonantimicrobial therapy plus matching placebo.

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

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

- **Delayed versus immediate therapy —** Patients in both study arms receive an active therapy, but administration of the comparator treatment is delayed relative to the experimental drug (i.e., one group is started on placebo but then switched to active therapy after a protocol-defined interval). Both groups remain blinded to treatment assignment for the entire study; to demonstrate efficacy, immediate therapy should be superior to delayed therapy.

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

A study design can be used where patients are enrolled at days 4 to 7 and a 3-day run-in period is used before randomization. Randomization of patients with symptoms that have not improved

[10] FDA review of previous ABECB-COPD studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD by antimicrobials (a precondition for a noninferiority trial). 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 study initiation. See also ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

over the 3-day run-in period may enrich the study population for patients with ABECB-COPD rather than a nonbacterial etiology for worsening of symptoms.

ABECB-COPD trials should be parallel group designs because crossover designs may be subject to carryover and period effects.

2. Study 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.

We recognize that it is not appropriate for patients with severe COPD (i.e., patients who are mechanically ventilated) to be enrolled in placebo-controlled studies of a new antibacterial for ABECB-COPD. We strongly encourage discussion with the appropriate review division if study of patients with severe COPD is being considered.[11] 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. Study Inclusion 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 are needed for study 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%, and FEV1 < 30% predicted or FEV1 < 50% plus chronic respiratory failure

[11] See section III.B.12., Ethical Considerations.

Spirometry may be difficult to perform at the time of an acute bacterial exacerbation of chronic bronchitis as 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 studies of ABECB-COPD. 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.

The specificity of sputum cultures for selecting patients with bacterial disease is unknown in ABECB-COPD since 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 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*).[12]

The following inclusion criteria should be used for patient enrollment in studies conducted for the treatment of ABECB-COPD.

a. 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 bronchitis (acute exacerbations) in the previous year
- History of tobacco use consistent with a diagnosis of COPD

b. Signs and symptoms

Signs and symptoms that can be present in patients with ABECB-COPD include the following:

- Dyspnea or breathlessness
- Cough
- Chest tightness or discomfort

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

- Sleep disturbances (i.e., insomnia or sleepiness)
- Decrease in exercise tolerance or limitation of usual activities
- Increase in sputum volume and/or sputum purulence
- Wheezing
- New or worsening crackles on auscultation of lung fields

Generalized signs and symptoms that are consistent with a diagnosis of ABECB-COPD (but are otherwise nonspecific) include:

- Fever (temperature greater than 38.5 degrees Centigrade)
- Malaise or fatigue
- Confusion or change in mental status

All signs and symptoms that may be present in patients with ABECB-COPD should be captured on the case report form, as should current tobacco use.[13]

4. Study Exclusion Criteria

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

- 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 (i.e., reversible obstruction of airflow with administration of bronchodilators by pulmonary function testing or a history of asthma).
- Patients with any concomitant illness that may confound the interpretation of the effect of study medications (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 study medications.

Sponsors may wish to exclude patients with a negative sputum culture at baseline; however, if these patients are included, stratification for this baseline characteristic should be included and the statistical analysis plan should include testing for the potential effect of a positive baseline culture. 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 prior antimicrobial use only if there is a positive sputum culture despite therapy. If patients who have received prior antimicrobial therapy are included, prior antibacterial drug therapy should be included as a stratification factor before enrollment.

[13] Use of a patient-reported outcome (PRO) instrument is recommended for capturing clinical response. PROs are discussed further in section III.B.9., Efficacy Endpoints.

5. Randomization, Stratification, and Blinding

Patients should be randomized for receipt of study drugs at enrollment. All studies should be double-blinded for study therapy.

6. Dose Selection

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

7. Choice of Comparators

As previously mentioned, only superiority trials for ABECB-COPD studies are recommended.[14] The control arm for these superiority studies can be placebo or another antibacterial drug.

8. Concomitant Medications

All patients should receive (or be receiving) bronchodilator and/or systemic corticosteroid therapy at the time of enrollment. 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 study groups but the reasons for administering concomitant medications differ. Confounding also may occur when the patients in one group who receive concomitant medications differ in baseline characteristics from those patients who do not receive concomitant medications. Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications during the study. 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 study.

We anticipate that changes in the use of the following medications will be monitored or specified in an ABECB-COPD study:

- 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 to all patients with a pre-enrollment FEV1 of < 50% of predicted FEV1

[14] See note 9, supra.

Assessment of the need for concomitant medications as an endpoint may not be an accurate surrogate for persistent patient signs or symptoms; the presence of such signs or symptoms should be confirmed by a patient-reported outcome (PRO) instrument that shows continued signs or symptoms at the time of administration of the concomitant medication. Efforts should be made to capture all concomitant medication use on a PRO instrument and to relate this information to patient signs or symptoms.

9. Efficacy Endpoints

a. Evaluation of clinical response

The primary emphasis of the study should be the effect of the antimicrobial drug on outcomes that are clinically important to patients. A well-defined and reliable method of assessing patient symptoms should be used for ABECB-COPD studies; accordingly, only use of a reliable PRO instrument is recommended as the primary outcome measure.[15] The PRO also should be used at baseline to define enrollment criteria; there should be a sufficient *score* on the PRO instrument such that a clinically meaningful response (i.e., change on the PRO instrument) can be observed. The amount of improvement 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 study initiation. Statistically significant differences between comparator regimens may not be sufficient for demonstrating benefit if response to treatment has not been confirmed to be clinically meaningful. 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 response instrument scale score.

If an adequate instrument is not available for studying ABECB-COPD, 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. If the plan is to enroll patients with very severe COPD or acute exacerbations, use of a caregiver-reported outcome instrument may be necessary when patients cannot respond themselves.

Assessment of clinical response at each time point should not be limited solely to symptoms identified at enrollment but should also capture symptoms that occur after study entry. A combined endpoint, including symptom assessment by a PRO instrument and other significant events (e.g., respiratory failure), is most appropriate in ABECB-COPD, with the expectation that the overall study result will be driven primarily by outcomes related to patient symptoms.

[15] The use of a well-defined and reliable PRO instrument, even for a categorical response, 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 draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

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

Since exacerbations are often associated with precipitous declines in airflow, the rapidity of recovery of a pulmonary function measures, such as FEV1, following an exacerbation to pre-exacerbation status also can be considered as an important possible primary efficacy endpoint. However, use of this endpoint involves the collection of recent pre-exacerbation FEV1 measurements.

A fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-resolution analysis. For example, clinical outcome at greater than 3 weeks after onset of therapy may not show a difference between treatment arms since 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 (e.g., the development of pneumonia should be considered a clinical failure) as part of the overall response assessment. 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 would now include *active* therapy for the placebo arm.

Objective measures such as peak expiratory flow or exercise testing (e.g., a *six-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 is needed in a placebo-controlled trial so that *rescue* therapy can be incorporated into the study 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

Since it is unlikely that patients will exhibit a complete resolution of symptoms, there should be no separate categories for success or relapse. However, patients who return to baseline at the end of study treatment can be assessed for the recurrence of symptoms that meet the study definition of ABECB-COPD. These patients should be evaluated (clinically and microbiologically) as would a new patient being entered into the study. This may be useful for studies that examine

recurrence as a secondary endpoint (i.e., assessment of the prolonged effect from antibacterial treatment of a single episode).

c. Adverse events or receipt of additional antibacterial therapy

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

Patients who receive another antibacterial drug while on study drug should be identified since these patients generally 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 and, therefore, should be viewed as being supportive information but not as a substitute for clinical outcome in a specific trial.[16]

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 since 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 studies with the bacteria.

10. Study Visits and Timing of Assessments

a. Entry visit

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

[16] Microbiological outcomes may be valuable in phase 2 studies 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) that will be evaluated in phase 3 studies.

- **History and demographic characteristics**

  - Date of visit.
  - Age, sex, and weight.
  - Underlying medical condition(s).
  - Current medications.
  - 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[17]
  - 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:

[17] 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 may be indicated in selected patients to exclude pulmonary embolism.

- A description of how the sample was obtained (e.g., expectoration, induced sputum, aspiration), processed, and transported to the laboratory.
- The adequacy of the specimen in terms of numbers of polymorphonuclear cells and epithelial cells present.[18]
- Identification of bacterial isolates.[19]
- In vitro susceptibility (preferably minimum inhibitory concentration) testing of the isolates to both the study 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.

If a positive sputum culture is used as one of the entry criteria for a clinical trial,[20] then no growth of pathogens on culture may allow exclusion of a significant number of patients whose exacerbation may be caused by factors other than bacterial infection (e.g., viruses, pollutants, allergens, cigarette smoke). Previous studies 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

Sputum culture data for *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* should be correlated with clinical outcome.

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., interview, interactive voice response via telephone, diary), the questioning of patients should be performed in a reproducible and structured way so that any potential biases in the method of

[18] 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 criteria: greater than 25 white blood cells per field at 100x magnification (low power, 10x objective) confirming the impression of *sputum purulence* and less than 10 squamous epithelial cells at 100x magnification (low power 10x objective).

[19] This information should remain blinded while the patient is receiving study medication.

[20] If it is believed that treatment should not be given unless patients are bacteriologically confirmed, then enrollment and treatment should be delayed until positive culture results return. If that is not the case, then an alternative is to enroll all patients at the time of presentation with screening by sputum gram stain, then analyze patients in the modified intent-to-treat (MITT) population. This situation is discussed further in section III.B.11., Statistical Considerations. We strongly recommend that patients enrolled at the time of screening continue to be followed per protocol, regardless of whether sputum culture is subsequently positive or not.

questioning do not affect study outcome.[21] The ability to detect differences between study therapies for a time-to-resolution endpoint may be increased if assessments are done more often (e.g., twice daily). Therapy should be continued as described in the study protocol regardless of whether symptoms have improved. Investigators should attempt to allow a minimum of 72 hours on therapy with the study medication before classifying a patient as a clinical failure; accordingly, investigators may wish to include a 48- to 72-hour visit to ensure there is not 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 arm; specific criteria to identify these patients should be included in the protocol. It is important that investigators distinguish patients who are worsening (i.e., where rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy. The protocol should also specify a failure endpoint if symptoms have not improved by a certain day on study, even if the symptoms are not clearly 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 antimicrobial therapy (or alternative antimicrobial therapy if appropriate) and/or other appropriate therapeutic modifications as necessary. 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 study 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 (e.g., history, physical examination, and laboratory test results) on the case report form. If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a well-defined and reliable diary is used to capture patient symptoms during this study visit, this information also should be recorded on the case report form.

c. Early follow-up visit

The early follow-up visit should occur after completion of all study medication at a time when the drug is expected to be clear from the infection site (usually at least 5 half-lives). For example, if a study drug with a short half-life is administered for 10 days, this study visit can occur on days 0 to 4 after completion of therapy; this study 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

[21] 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 draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.)

should inquire about adverse events. Depending on the study 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 study medication (e.g., if study drug is administered for 10 days, this assessment can occur on days 20 to 25 after initiation of therapy (unless a drug with a long $t_{1/2}$ 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. All adverse events should be followed to resolution.

e. Safety evaluations

The protocol should clearly specify the methods to be used to obtain safety data during the course of the study. Both adverse event information and safety laboratory data should be collected during the study. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations also may be needed because of the preclinical and clinical profile of the specific drug under study (e.g., additional electrocardiogram measurements). Longer-term assessment of adverse events after discontinuation or completion of the 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 study visit or assessment, regardless of whether the test drug has been discontinued.[22] All adverse events should be followed until resolution, even if time on study would otherwise have been completed.

11. Statistical Considerations

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

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

643 a. Analysis populations
644
645 The following definitions apply to various populations for analyses in ABECB-COPD clinical
646 trials:
647
648 • **Safety population —** All patients who receive at least one dose of assigned therapy
649 during the study.
650
651 • **Intent-to-treat (ITT) population** — All patients who are randomized.
652
653 • **Modified intent-to-treat (MITT) population (also sometimes referred to as**
654 **microbiological intent-to-treat population) —** All patients who are randomized and
655 who have a pathogen associated with ABECB-COPD isolated at baseline. Patients
656 should not be excluded from this population based upon events that are measured post-
657 randomization (e.g., loss to follow-up). If a positive culture is required for study entry,
658 this population is identical to the ITT population.[23]
659
660 • **Per-protocol populations (also referred to as the *clinically evaluable* or**
661 ***microbiologically evaluable* populations) —** The population of patients who meet the
662 definition for the primary analysis population (ITT or MITT population) and who follow
663 important components of the protocol as specified (e.g., administration of a specified
664 minimum amount of study medication). Traditionally, adequacy of therapy for a per-
665 protocol analysis population has been defined as patients who have received greater than
666 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or dosing
667 regimen. Sponsors should document compliance with dosing (e.g., daily assessment,
668 patient diary, urine testing, or MEMS caps).
669
670 To ensure consistency of results, the ITT and/or MITT populations in the study should be
671 evaluated as well as the population of patients who follow important aspects of the protocol (i.e.,
672 the per-protocol populations). However, it is also important to note that the per-protocol
673 population analyses are subgroup analyses since they exclude patients based upon events that
674 occur after randomization. Patients in such subgroup analyses may differ by important factors
675 (both measured and unmeasured) other than the drug received; because of this, analyses based on
676 the ITT (or MITT) population should be considered the primary study analyses, with analyses
677 based on a per-protocol population reviewed for consistency of results. Results in both
678 populations should provide evidence of effectiveness.
679
680 The primary and secondary analyses should be defined in the protocol before starting the study.
681 Depending on the exact hypothesis being tested, sponsors may prefer to specify either the ITT or
682 MITT population as the primary population for analysis; for example, if patients are enrolled
683 before results of the sputum culture return but the primary hypothesis is that an effect is most
684 likely to be seen in patients with *S. pneumoniae* or other likely pathogens isolated, then the study
685 should be powered for the MITT population and this should be the primary analysis. If it is
686 expected that the treatment arm will be superior to the placebo arm for all patients enrolled, even

[23] The culture results (i.e., the specific bacterial organisms) that define whether a patient should be included in the MITT population should be stated in the protocol.

including 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., MITT or ITT) for the primary analysis may guide the details of product labeling if the drug is approved.

b. Noninferiority margins

As mentioned, FDA review of previous ABECB-COPD studies 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, noninferiority trials currently are not considered adequate to establish evidence of effectiveness for regulatory approval of a new indication for ABECB-COPD. For additional information regarding noninferiority studies in general and in antibacterial trials, see ICH E10 and the draft guidance for industry *Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval*.[24]

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 study. 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 study 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 MITT 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 study 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 study 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 study report.

e. Interim analyses and data and safety monitoring boards

If interim (or futility) analyses will be performed, they should be specified in the analysis plan. The purpose of the interim analysis should be clearly stated in the analysis; it is important that the interim analysis does not affect study conduct and thereby compromise study results. Study data also should be examined at the time of interim analysis for any emerging safety signals. We

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

encourage sponsors to discuss their plans with the review division before initiation of the trial to ensure that the overall study significance tests properly address the effect of interim testing.

Use of a data and safety monitoring board (DSMB) may be appropriate depending on the design of the proposed phase 3 trial and the patient population that the trial will enroll. If a DSMB is used, a detailed charter with the composition of the committee members and the operational details should be provided for review.[25]

f. Other analyses of interest and secondary endpoints

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

If a statistical analysis plan is developed to expand on the details of the analysis from that in the protocol, the sponsor should submit the analysis plan for any phase 3 ABECB-COPD study to the FDA before initiation of the trial.[26]

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

12. Ethical Considerations

Review of previous placebo-controlled studies of the treatment of ABECB-COPD has shown variable results, with several placebo-controlled studies showing no effect for antimicrobial treatment of exacerbations. Accordingly, for patients with mild to moderate disease, studies 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 since low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. The occurrence of common but less-severe adverse events (e.g., diarrhea) from antibacterial drugs also can be relevant in assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment effect may be small. Rescue therapy can be incorporated into the study design so that individual

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

[26] For more detailed information, see the draft guidance for industry *Developing Antimicrobial Drugs — General Considerations for Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

patients are treated at the time a failure outcome is assigned; this addition may serve to mitigate concerns regarding inclusion of a placebo arm in an ABECB-COPD trial. All study designs should provide appropriate provisions for patient safety.

Although study results have been varied, some prior studies of ABECB-COPD have shown clinically significant benefit in severely ill patients. We strongly encourage discussion with the appropriate review division regarding design of placebo-controlled studies 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

Currently, 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

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]."*

3. Antimicrobial Resistance Claims

To date, the FDA has not granted resistance claims for ABECB-COPD caused by antimicrobial resistant bacteria. To propose a claim for antimicrobial resistant pathogens in ABECB-COPD, data from within the clinical trials should be presented that clearly demonstrate the adverse clinical effect(s) of in vitro resistance and the ability of the study antimicrobial to significantly reduce or eliminate the adverse clinical effect(s). If resistance is mediated by different mechanisms within the same class of resistance (e.g., extended-spectrum beta-lactamases), the effect of the study drug to eliminate bacteria with the various different mechanisms of resistance should be demonstrated clinically. Resistance claims should be relevant to ABECB-COPD (e.g., amoxicillin resistance is more clinically relevant than penicillin resistance since the latter is rarely prescribed for ABECB-COPD). Sponsors seeking resistance claims should contact the review division before initiating clinical trials to discuss appropriate study designs that may be suitable to achieve the desired resistance claims.