Guidance for Industry

Exercise-Induced Bronchospasm (EIB) — Development of Drugs to Prevent EIB

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
February 2002
CMC

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I. INTRODUCTION

This guidance is intended to assist sponsors in designing clinical development programs to achieve an indication for the prevention of exercise-induced bronchospasm (EIB). Drugs that are given chronically to control asthma may also lessen the propensity to develop EIB, as a general consequence of decreasing bronchial hyperreactivity. An important distinction is made, however, between such chronically administered drugs and shorter acting drugs that are given acutely to prevent EIB. This guidance provides recommendations for sponsors who are interested in developing drugs that are given acutely to prevent EIB.

II. BACKGROUND

In many patients, better control of their asthma will prevent or lessen the severity of EIB. Chronically administered asthma *controller* therapies, therefore, will have beneficial effects on EIB in many subjects. Examples of such therapies include the corticosteroids and the leukotriene inhibitors. Clinical studies can be performed with such products to demonstrate a benefit in ameliorating the symptoms of EIB over time. This information can also be considered for description in the clinical trials section of the label, depending on substantiation and other factors. Currently, the Division does not believe that a separate indication statement specifically for the prevention of EIB is appropriate for such products. Furthermore, labeling of such products may appropriately caution against the use of chronically administered drugs solely for the prevention of EIB. While this guidance document provides helpful information on the conduct of EIB trials, it is not intended to address exercise-related study designs for these more chronically administered types of asthma therapies.

[1] This guidance has been prepared by the Division of Pulmonary Drug Products (the Division) in the Center for Drug Evaluatiion and Research (CDER) at the Food and Drug Administration (FDA).

To achieve an indication for the prevention of EIB, a drug should be given acutely and should be administered just before exercise to prevent EIB. Examples of such therapies include the inhaled short-acting and longer acting beta agonist bronchodilators and inhaled cromolyn sodium. This guidance document is intended to provide trial design suggestions to help guide sponsors of such products who seek an indication for the prevention of exercise-induced bronchospasm.

III. OVERALL CONSIDERATIONS

The clinical development program outlined in this guidance document pertains to a new drug moiety or a drug that does not already carry the EIB indication, but for which the sponsor would like to obtain that indication. For drugs that are reformulations of a reference product that already has the EIB indication, a full EIB program may not be necessary, depending on the extent of the changes in the product and the dose-ranging data available with that product. Sponsors of such reformulated drug products are encouraged to discuss their approach for supporting an EIB indication with the Division.

A. Number of Trials

To obtain an EIB indication in adults and adolescents age 12 and older, two placebo-controlled clinical trials that demonstrate efficacy should generally be conducted. It is anticipated that the demonstration of safety for a drug to prevent EIB will already be known from longer-term studies that have been performed to obtain an asthma indication and from such studies that supported the approval of that drug for asthma.

To obtain an EIB claim in pediatric patients under age 12, a single adequate, placebo-controlled clinical trial involving a range of appropriate doses may be sufficient, as long as the indication is already established in adolescents and adults. Pediatric data from at least one EIB trial are important for identifying the correct pediatric dose for this indication. It may be appropriate for children to take a different nominal dose compared to adolescents and adults. Also, children may not master a given device as readily as adults, or they may not be able to generate the inspiratory flow rates called for in optimal drug delivery. Therefore, pediatric EIB data should be generated with a dose-ranging trial incorporating appropriate doses for the population.

B. Trial Design

Whenever possible, it is recommended that trials be double blind and placebo controlled. A crossover study design has been commonly employed in EIB programs and is appropriate. The suitable washout between treatment periods depends on the half-life of the study drug. The washout period could be as short as a few days for a short-acting drug (such as inhaled albuterol), while longer acting drugs (such as inhaled salmeterol) may call for washout periods of 3 days or longer. An active control arm, if added, may provide useful perspective on the degree of efficacy seen with the test drug, as well as the relative onset and duration of action. If comparative claims against an active drug are desired, sponsors should discuss this in advance with the Division. Ordinarily, any comparative claims should be replicated.

C. Timing of Drug Administration Prior to Exercise

The dosage and administration section of the package insert will recommend use of the product based on how it was studied in the clinical trials. For example, if a drug was administered 15 minutes before exercise in the clinical trials and showed benefit, the drug would likely be recommended for use 15 minutes before exercise. Pharmacokinetic information, such as the time of maximal drug concentration, or pharmacodynamic information, such as the time of peak bronchodilation, may be helpful in determining the most appropriate timing for drug administration prior to exercise.

D. Dose Response and Safety With Chronic Use

In general, it is anticipated that dose responsiveness, as well as safety of chronic exposure to the drug, has already been demonstrated when the drug was approved for the treatment of asthma. In such cases, additional safety data may not be necessary for the EIB indication, and more limited dose-response examination may be appropriate. However, if dose responsiveness and safety data related to chronic exposure are unknown, studies should generally be included to address these issues.

E. Duration of Protection Against EIB

Sponsors are encouraged to evaluate the presence or absence of protection from EIB for the anticipated duration of action of the study drug following a single dose of study drug. Exercise challenge tests should be conducted at intervals that define when clinically meaningful protection is no longer obtained. The total number and spacing of exercise challenges for any given drug therefore depends on its anticipated onset of action, as well as its anticipated duration of effect. From this information, the package insert can convey the appropriate timing of study drug administration prior to exercise, as well as the expected duration of effect.

It is important to note that the sensitivity to exercise challenge may decrease with repeated episodes of exercise (50% of individuals with EIB are refractory to a second challenge within 50 minutes). Therefore, the exercise challenges should be spaced appropriately, and the total number of challenges in any single crossover period should be limited. If that approach is not feasible, an alternative approach would be to perform two separate studies for a drug that is anticipated to provide a long duration of protection. One study would evaluate early protection (e.g., challenges within the first few hours after study drug administration), and a second study would evaluate later protection (e.g., challenges at more prolonged time points).

F. Efficacy With Chronic Use

Concerns about chronic use arise when a drug is developed to be used both *regularly* for the maintenance treatment of asthma, and *as needed* for the prevention of EIB. Many patients with EIB may use an as-needed therapy almost daily if they exercise on a frequent basis. It is relevant for such patients to know whether the anticipated protective benefit of the drug is maintained when the drug is used semiregularly or regularly over time. Furthermore, it has become apparent that the degree of protection with some drugs that prevent EIB may diminish when the drug is

used chronically. Although labeling for such drugs could specify that the use of the drug for prevention of EIB is not recommended when the drug is being regularly administered for maintenance of asthma, it is nonetheless likely that such use may occur in reality. Therefore, it may be appropriate to conduct studies to evaluate the degree of EIB protection over time with chronic administration. Such studies could use a crossover study design but would evaluate subjects after initial use of the study drug, as well as after a more chronic period of use.

IV. SPECIFIC TRIAL CONSIDERATIONS

A. Inclusion and Exclusion Factors

Sponsors should consider certain characteristics when selecting patients to participate in their studies. It is recommended that nonsmokers (i.e., not currently smoking and with a 10-pack per year history or less of smoking) with a history of EIB be enrolled. Patients can have either symptoms of EIB alone, or they can have a diagnosis of asthma with additional symptoms of EIB. Asthmatics should be stable, requiring only the occasional use of inhaled beta agonists for symptoms. Patients who have had an asthma exacerbation or recent upper respiratory infection during the 4 weeks prior to enrollment should be excluded. Consideration should be given to excluding patients with seasonal asthma, since the onset of a season during the crossover trial might affect the validity of the study results. Consideration should also be given to excluding patients taking antihistamines (particularly if they are taking them *as needed*) since this could also confound the interpretation of the crossover study. At screening, patients should have a predicted FEV_1 of at least 70 percent, and should demonstrate a decrease in FEV_1 with exercise of at least 20 percent from their baseline absolute FEV_1 value. Patients who require rescue medication following exercise or whose FEV_1s fall precipitously should be excluded from randomization.

B. Prior Use of Medications

Medications taken before study entry could affect the validity of study results. Patients should be restricted from enrollment if they have received parenteral or oral corticosteroids during the 12 weeks before study entry. Patients taking inhaled or other topical corticosteroids and leukotriene inhibitors could be either excluded or included if these medications were taken during the 4 weeks before study entry. If included, however, the patients' dosage for such medications should have been stable for the 4 weeks prior to study entry. Patients should be able to withhold the use of short-acting bronchodilators (such as inhaled albuterol) during the 8 hours before testing and long-acting bronchodilators (such as inhaled salmeterol) during the 48 hours before testing.

Additional restrictions to consider include limiting any allowed caffeine use, the timing of last exercise or strenuous activity, and the timing of last exposure to cold air.

C. Exercise Testing[2]

Generally, not more than four exercise challenges are recommended poststudy drug administration, since patient response to exercise may wane with multiple challenges in a short time frame. A shorter acting drug can have fewer exercise challenges that are more tightly spaced, whereas a longer acting drug can have more challenges that are spaced out over time. Serial spirometry should be performed starting pre-exercise and at 5, 10, 15, 30, and 60 minutes following each exercise challenge. Triplicate determinations of FEV_1 should be performed with each test, with the highest reading recorded for analysis.

D. Efficacy End Points and Analyses

FEV_1 is an appropriate primary outcome variable, particularly in adults and adolescents. Two analyses of this variable are recommended, and each analysis should provide an important perspective on efficacy. The Division will consider alternative end points, particularly for a younger pediatric patient population. However, these end points should be discussed in advance with the Division.

For study drug (versus placebo), the primary efficacy analysis should compare the maximum percentage fall in FEV_1 from baseline that is documented at any time point within the first hour following exercise. Baseline FEV_1 is defined as the FEV_1 obtained just before each exercise challenge test. Pulmonary function tests should be performed at 5, 10, 15, 30, and 60 minutes postexercise. The maximal fall in FEV_1 should be recorded for each patient, and the mean maximum fall in FEV_1 should be reported for the patients treated with study drug as well as placebo. To assess the full duration of protection, analyses should be repeated for each serial exercise challenge that is performed following study drug administration.

An important secondary analysis of FEV_1 is to categorize for each treatment the percentage of patients whose FEV_1 falls by a specified amount from baseline. For example, these categories can be divided into groups of patients whose FEV_1 fell according to the following percentages in the first hour after each exercise challenge: (1) by less than 10 percent of the prechallenge baseline (i.e., no response or minimal response), (2) between 10 to 20 percent (i.e., intermediate response), and (3) by more than 20 percent (i.e., a positive response). This presentation should be given for each crossover sequence separately, as well as combined over both crossover sequences. These analyses provide important perspectives on the individual patient response and are believed to be complementary to the mean maximum percentage fall in FEV_1 analysis. If a drug (versus placebo) shows a statistically significant effect for the primary analysis of mean maximal percentage fall in FEV_1 for the group, but the drug fails to show a meaningful improvement in patient responses for the categorical analysis, the results would be a review issue of concern.

[2]For guidance on exercise testing, sponsors can refer to the American Thoracic Society's (ATS's) "1999 Guidelines for Methacholine and Exercise Challenge Testing," *Am J Resp Crit Care Med* 161 (2000): 309-329 (available on the Internet at www.thoracic.org/statements).

E. Safety Considerations

In general, it is anticipated that the safety profile of the drug will be known if the drug has been otherwise studied for the treatment of asthma. In this case, safety evaluations could be fairly limited in the shorter-term EIB clinical trials. Such safety evaluations could, however, include laboratory evaluations, electrocardiograms, physical findings including vital signs, and monitoring for any adverse events.

The primary safety concern in EIB trials is the occurrence of severe bronchoconstriction. Patients who experience a fall in FEV_1 of more than 40 percent from baseline should receive rescue treatment with a standard dose of an acute bronchodilator. If such patients do not return to an FEV_1 that is at least within 20 percent of their baseline, they should not continue in the exercise protocol.