DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 021929

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Connie Hickman
Associate Director, Regulatory Affairs

Dear Ms. Hickman:

Reference is made to your October 1, 2010, Proposed Pediatric Study Request for budesonide and formoterol.

BACKGROUND:

These studies will investigate the potential use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate in an HFA-pressurized metered-dose inhaler (pMDI) for the treatment of asthma in children aged 6 to <12 years not adequately controlled on inhaled corticosteroids (ICS). Asthma is a chronic inflammatory disorder of the airways and a leading chronic disease in children. In 2004, asthma affected approximately 6 million children and adolescents <18 years of age in the United States.

Approved medications used to control asthma include single-ingredient ICS, fixed dose ICS and long-acting beta$_2$-agonists (LABAs) combination products, single ingredient LABAs + single ingredient ICS, and leukotriene inhibitors and antagonists. Single-ingredient budesonide is approved as an ICS in a dry-powder formulation and as a suspension for nebulization, and formoterol is a LABA approved in a dry-powder formulation for the treatment of asthma in children <12 years of age. The fixed-dose combination of budesonide and formoterol fumarate dihydrate in an HFA pMDI is currently approved for adults and pediatric patients 12 years of age and older. However, the individual ingredients (budesonide and formoterol) are not approved in a pMDI formulation. Since a LABA should only be added to treatment of patients not adequately controlled on a long-term asthma control medication such as an ICS, the dose of budesonide used in the fixed-dose ICS/LABA combination product must be a dose that as a single ingredient would be safe and efficacious in patients whose disease severity requires treatment with single-ingredient ICS therapy. Information is already available to support the safety of budesonide in this age group at doses as high as 680 mcg per day of the HFA MDI formulation.

The studies outlined in this Written Request are designed to evaluate the appropriate dose of budesonide in an HFA pMDI (Study 1) and evaluate the appropriate dose of formoterol in an HFA pMDI (Study 2) to be carried into an efficacy and safety trial of the fixed-dose combination of budesonide and formoterol in an HFA pMDI (Study 3). Study 3 is a factorial design study to demonstrate the contribution of the addition of formoterol in the fixed-dose combination. Because of the safety concerns with LABAs when used as single ingredients, and because of the safety concerns with the use of placebo in this population, single-ingredient LABA and placebo arms are not included in this study. Should this product receive an indication for use in patients with asthma 6 to <12 years of age, the product would be subject to the postmarketing requirement in effect for the currently approved budesonide/formoterol fumarate HFA pMDI product in older age groups.

To obtain needed pediatric information on this fixed-dose combination of budesonide and formoterol fumarate dihydrate in an HFA pMDI, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  Study 1: A double-blind, randomized, parallel-group, placebo-controlled, efficacy and safety study in children aged 6 to <12 years with asthma, comparing budesonide delivered in an HFA pMDI formulation with placebo. The duration must be at least 6 weeks, and the dose of budesonide chosen for evaluation must be a dose that could provide a safe and efficacious dose of budesonide as a single-ingredient HFA pMDI formulation.

  Study 2: A randomized, blinded, 5-period cross-over, placebo and active-controlled, dose-finding study evaluating the bronchodilating effects and safety of single doses of formoterol delivered via Symbicort HFA pMDI in children ages 6 to <12 years with asthma who are receiving background treatment with budesonide delivered in an HFA pMDI formulation. The study must include at least 3 doses of formoterol fumarate HFA pMDI, and the active control must use a formulation and dose of formoterol that is approved in this age group.

  Study 3: A double-blind, parallel-group, 12-week study of 2 doses of Symbicort pMDI compared with the corresponding dose or doses of budesonide monotherapy delivered in a HFA pMDI formulation, to determine the efficacy and safety of Symbicort HFA pMDI in pediatric patients ages 6 to <12 years. The dose(s) of budesonide chosen for evaluation must be dose(s) that could be safe and efficacious as a single-ingredient HFA pMDI formulation.

Studies 1 and 2 must be completed before Study 3 in order to define the appropriate doses to be used in Study 3.

- *Objective of each study:*

  Study 1: To determine the appropriate dose(s) of budesonide HFA pMDI for pediatric patients 6 to <12 years of age to be carried into the combination product.

  Study 2: To determine the appropriate dose(s) of formoterol HFA pMDI for pediatric patients 6 to <12 years of age to be carried into the combination product. The study will evaluate at least 3 doses of formoterol fumarate in an HFA pMDI formulation to find a dose that provides comparable bronchodilation with that of an approved formulation and dose of formoterol fumarate in this age group.

  Study 3: To demonstrate the efficacy and safety of Symbicort HFA pMDI as a fixed-dose combination containing budesonide and formoterol compared with the corresponding dose or doses of budesonide HFA pMDI monotherapy, each administered as 2 inhalations twice daily, in children aged 6 to <12 years not adequately controlled on low-dose ICS. The dose or doses of budesonide and formoterol to be used in Study 3 will be determined by the results of Studies 1 and 2.

- *Patients to be studied:*

  - *Age group in which study(ies) will be performed*: Children aged 6 to <12 years who are symptomatic on ICS.

  - *Number of patients to be studied:*

  Study 1: A minimum of 133 patients per treatment group (2 or more groups) must be randomized and treated with at least one dose of study treatment.

  Study 2: An adequate number of patients must be randomized to obtain a minimum of 50 completed patients (patients who completed all treatment periods).

  Study 3: A minimum of 115 patients per treatment group (3 or more groups) must be randomized and treated with at least one dose of study treatment. Randomization should be stratified by age group (children under 8 years of age versus children 8 years and older) with approximately equal number of patients in each age group.

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Study 1: Efficacy endpoints must include changes from baseline in pre-dose morning peak expiratory flow (PEF) rate and in pre-dose morning forced expiratory volume in the first second (FEV_1). Other efficacy variables must include spirometry, asthma symptom scores, nighttime awakenings due to asthma symptoms, use of reliever medication, and the number of withdrawals due to predefined criteria for worsening of asthma. Safety variables must include adverse events (AEs), discontinuations due to adverse events (DAEs), serious adverse events (SAEs), vital signs (blood pressure, pulse, and respiratory rate), physical examinations, and pre-defined asthma worsening criteria requiring clinic evaluation by the investigator to determine if the patient can continue in the study.

  Study 2: Efficacy endpoints must include the area-under-the-curve from 0-12 hours (AUC_{0-12}) for FEV_1, the FEV_1 at 12 hours after study medication inhalation, and the maximal FEV_1 for the 12-hour study period. The pharmacokinetics endpoint must be the 12-hour urinary unchanged formoterol. Safety endpoints must include AEs, DAEs, SAEs, vital signs (heart rate and blood pressure), and physical examinations.

  Study 3: Efficacy endpoints must include changes from baseline in pre-dose morning PEF and FEV_1. Other efficacy variables must include other spirometric measures, asthma symptom scores, nighttime awakenings due to asthma symptoms, use of reliever medication, and the number of withdrawals due to predefined criteria for worsening of asthma. Safety endpoints must include AEs; DAEs; SAEs; vital signs; physical examinations; post-dose ECG, blood glucose, serum potassium, and signs and symptoms of adrenergic stimulation such as irritability, tremor, lack of sleep; and pre-defined asthma worsening criteria requiring clinic evaluation by the investigator to determine if the patient can continue in the study.

- *Known drug safety concerns and monitoring:*

  Safety concerns with inhaled corticosteroids include local effects such as oropharyngeal fungal infections (i.e., *Candida albicans)*, growth suppression, glaucoma and cataracts, decreased bone mineral density, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Monitoring for safety concerns must be performed in the clinical trials, as listed under the Study Endpoints section above.

  Safety concerns with LABAs include asthma-related death, increased hospitalizations metabolic effects including hypokalemia and hyperglycemia, signs and symptoms of adrenergic stimulation, and effects on coexisting conditions such as cardiovascular or central nervous system disorders. Monitoring for safety concerns must be performed in the clinical trials, as listed under the Study Endpoints section above.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller

sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form:* HFA pressurized metered-dose inhaler (pMDI)
  - *route of administration:* orally inhaled
  - *regimen:* two inhalations twice daily

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

  Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

  For all three studies, the primary analysis of efficacy should be based on an analysis set that includes all randomized patients who took at least 1 dose of study medication.

  Study 1: For morning PEF, a sample size of 133 per treatment group will have 90% power to detect a difference in means of 12 L/min assuming that the common standard deviation is 30 L/min at the 0.05 significance level. For pre-dose FEV_1, a sample size of 133 per treatment group will have 90% power to detect a difference in means of 0.09 L in FEV_1 assuming that the common standard deviation is 0.23 L at the 0.05 significance level.

  The efficacy endpoints must be AM pre-dose PEF and morning pre-dose FEV_1, and each should be analyzed using an ANCOVA model with terms for treatment, country and age group, and baseline value (i.e., morning PEF and pre-dose FEV_1, respectively) as a covariate. Multiplicity should be addressed using a hierarchical testing procedure starting with AM PEF. If the result for AM PEF is statistically significant at the 0.05 level of significance, then test FEV_1 at the 0.05 level of significance.

  Study 2: An adequate number of patients aged 6 to <12 years with a clinical diagnosis of asthma will be randomized to reach approximately 50 completed patients. Approximately 25% of completed patients will be children under the age of 8 years. A sample size of 51 will have 90% power to detect a difference in treatment group means of 0.065 L assuming a standard deviation of differences of 0.14 L.

  The efficacy endpoint of the average change from baseline in 0-12 hours (AUC_{0-12}) for FEV_1 should be analyzed with an ANCOVA model appropriate for a crossover design. Multiplicity for the 3 doses of formoterol should be addressed by applying a multiple comparison procedure (e.g., Dunnett's test).

  Study 3: The sample size is based on the larger of the two estimates described below, namely that for FEV_1. For AM PEF, a sample size of 86 per treatment group will have 90% power to detect a difference in means of 15 L/min, assuming that the common standard deviation is 30 L/min at the 0.05 significance level. For predose FEV_1, a sample size of 115 per treatment group will have 90% power to detect a difference in means of 0.10 L in FEV_1, assuming that the common standard deviation is 0.23 L at the 0.05 significance level.

  The efficacy endpoints must be AM pre-dose PEF and morning pre-dose FEV_1, and each should be analyzed using an ANCOVA model with terms for treatment, country and age group, and baseline value (i.e., morning PEF and pre-dose FEV_1, respectively) as a covariate. Multiplicity should be addressed using a hierarchical testing procedure starting with the higher dose:

  1. Test the higher dose of Symbicort pMDI vs. Budesonide pMDI for AM PEF at the 0.05 level of significance. If the result is statistically significant, then:

2. Test the higher dose of Symbicort pMDI vs. Budesonide pMDI for FEV_1 at the 0.05 level of significance. If the result is statistically significant, then:
3. Test the lower dose of Symbicort pMDI vs. Budesonide pMDI for AM PEF at the 0.05 level of significance. If the result is statistically significant, then:
4. Test the lower dose of Symbicort pMDI vs. Budesonide pMDI for FEV_1 at the 0.05 level of significance.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that a fixed-dose combination of budesonide and formoterol fumarate dihydrate in an HFA pressurized metered-dose inhaler is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All postmarket reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the postmarket adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before March 31, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Curtis J. Roseebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
01/28/2011