DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022518

WRITTEN REQUEST

Merck Sharp & Dohme Corp.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889

Attention: Michele Flicker, MD PhD
Executive Director, Global Regulatory Affairs

Dear Dr. Flicker:

Reference is made to your March 20, 2012 Proposed Pediatric Study Request (PPSR), the July 23, 2012, Written Request issued by the Agency, your January 18, 2013, Response to Written Request indicating that you would be declining the Written Request, and your March 30, 2017, PPSR to issue a new Written Request for mometasone furoate and formoterol fumarate.

BACKGROUND:

This study will investigate the potential use of a fixed-dose combination of mometasone furoate and formoterol fumarate in a hydrofluoroalkane (HFA)-pressurized metered-dose inhaler (pMDI) for the treatment of asthma in children 5 to 11 years not adequately controlled on inhaled corticosteroids (ICS).

Asthma is a chronic inflammatory disorder of the airways and a leading chronic disease in children with an estimated prevalence of asthma in children 0-17 years of age of 9.6 %.[1] Approved medications used to treat asthma include single-ingredient inhaled corticosteroids (ICS), fixed-dose ICS and long-acting beta2-agonists (LABAs) combination products, single-ingredient LABAs + single-ingredient ICS, leukotriene antagonists, anticholinergics, methylxanthines, and anti-IgE and anti-IL-5 antibodies.

Single-ingredient mometasone furoate is an ICS approved as a dry powder inhaler (DPI) formulation down to the age of 4 years and as a pMDI down to 12 years of age. Single ingredient formoterol is a LABA approved in a DPI formulation for the treatment of asthma in children down to 5 years of age, but is contraindicated for use as a monotherapy (i.e. without a long term asthma control medication) such as an ICS. The individual ingredient formoterol is not approved in a pMDI formulation. The fixed-dose combination of mometasone furoate and

[1] Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality; United States, 2005-2009. National health statistics reports; no 32. Hyattsville, MD: National Center for Health Statistics. 2011.

formoterol fumarate in an HFA pMDI is currently approved for adults and pediatric patients 12 years of age and older.

The study outlined in this Written Request is designed to provide evidence of efficacy and safety for use of this fixed-dose combination in children 5 to 11 years of age. Studies in patients <5 years of age, including neonates, are considered unnecessary because the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used.

To obtain needed pediatric information on this fixed-dose combination of mometasone furoate and formoterol fumarate 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 non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical study:*

  A randomized, double-blind, parallel-group, 12-week study with a 12-week safety extension evaluating the efficacy and safety of one dose of mometasone furoate/formoterol fumarate HFA pMDI compared to the corresponding dose of mometasone furoate in an HFA pMDI formulation in pediatric patients ages 5 to 11 years who are symptomatic on ICS. The dose of mometasone furoate chosen for evaluation must be a dose that is safe and efficacious as a single- ingredient HFA pMDI formulation.

- *Objective of the study:*

  To demonstrate the efficacy and safety of mometasone furoate and formoterol fumarate in a HFA pMDI compared with the corresponding dose of mometasone furoate HFA pMDI monotherapyin children ages 5 to 11 years not adequately controlled on ICS.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*: Children aged 5 to 11 years.

  - *Number of patients to be studied:*

    The study will include a sufficient number of enrolled patients to produce a sample size adequately powered for detecting treatment differences between the fixed-dose combination and the single-ingredient mometasone HFA pMDI monotherapy based on estimates of the effect size of the primary efficacy endpoint. Approximately 20% or more of randomized patients should be children

under the age of 8 years and approximately evenly distributed between the ages of 5 and 8. Patients should remain on their assigned, blinded treatment arms for the 24-week duration of the study. In addition, the study will include a sufficient number of patients to complete a safety database of at least 80 patients with exposure to mometasone furoate/formoterol fumarate HFA pMDI and 80 to mometasone furoate HFA pMDI for 24 weeks.

Representation of Ethnic and Racial Minorities: The study 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:*

  The primary efficacy endpoint must include the change from baseline in AM post-dose % predicted FEV1. Serial post-dose spirometric measures should also be evaluated and blood samples should be collected for measuring mometasone furoate plasma concentration in a subset of patients.

- *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, increased intraocular pressure, glaucoma, cataracts, decreased bone mineral density, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Monitoring for safety concerns must be performed in the clinical trials.

  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.

- *Extraordinary results:* In the course of conducting this study, 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:* oral inhalation

- *regimen:* two inhalations twice daily

  Use an age-appropriate formulation in the study 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.

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

The study must have a pre-specified, detailed statistical analysis plan appropriate for the study design and outcome measures, and this plan must be submitted prior to the start of the study. The study will be designed to provide at least 80% statistical power to detect a treatment effect, at a conventional statistical significance level (two sided $\alpha = 0.05$). A clinically meaningful effect size will be pre-specified, justified in the protocol, and must be discussed with and agreed upon by the FDA prior to initiating the study. The statistical analysis plan should include information addressing the issue of missing data, clearly specifying an estimand and associated sensitivity analyses for the key efficacy endpoints. Patient disposition tables should clearly distinguish between discontinuation of treatment and withdrawal from study, and reasons for discontinuation of treatment or withdrawal from the study should be recorded, avoiding less informative terms such as 'lost to follow-up,' 'patient/investigator decision,' 'withdraw consent,' in favor of categories relevant to safety or effectiveness, such as 'treatment ineffective' or 'adverse reaction.' Refer to The Prevention and Treatment of Missing Data in Clinical Trials by the National Research Council.[2] The analysis plan should also incorporate methods to control type I error in the face of multiple primary efficacy endpoints. You should employ test procedures with underlying assumptions more robust than the Hochberg method.

Safety data will be summarized by descriptive statistics.

[2] The Prevention and Treatment of Missing Data in Clinical Trials. National Research Council. 2010. The National Academies Press

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrates that a fixed-dose combination of mometasone furoate and formoterol fumarate dehydrate in an HFA pMDI 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. 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 post-market 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 post-market 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 February 21, 2019. 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) must 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, CDER, FDA, Document Control Room, Metro Park North VII, 7620 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 Ji Hyun LaRose, Regulatory Project Manager, at 301-796-9017.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D. M.P.H
Director
Office of Drug Evaluation II
Office of New Drugs
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
12/04/2017