NDA 204275

WRITTEN REQUEST – AMENDMENT 2

GlaxoSmithKline Intellectual Property Development Ltd. England
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Attention: Patrick D. Wire, PharmD
Director, Regulatory Affairs

Dear Dr. Wire:

Please refer to your correspondence dated February 21, 2020, requesting changes to FDA's December 20, 2017, Written Request for pediatric studies for Breo Ellipta (fluticasone furoate and vilanterol Inhalation Powder).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on December 20, 2017, and as amended on May 30, 2018, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before ~~July 30, 2021~~ July 31, 2023.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 20, 2017, as amended by this letter and by previous amendment dated May 30, 2018, must be submitted to the Agency on or before July 31, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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.

In accordance with section 505A(k)(1) of the Act, 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:

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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Elaine Sit, Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Complete Copy of Written Request as Amended

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

Complete Text of Written Request As Amended

BACKGROUND:

This study will investigate the potential use of a fixed-dose combination of fluticasone furoate and vilanterol inhalation dry powder in the treatment of asthma in children 5 to 17 years of age not adequately controlled on inhaled corticosteroids.

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 %.[2] 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, anti-IgE, and anti-IL-5 antibodies.

Single-ingredient fluticasone furoate is an ICS approved as an inhalation dry powder for the once-daily maintenance treatment of asthma in patients 12 years of age and older. Pediatric efficacy and safety studies evaluating fluticasone furoate in asthmatic patients 5 to 11 years of age have been completed and are currently under review by the Agency. Single-ingredient vilanterol is not approved for use in the United States for any indication in any age group. The fixed-dose combination of fluticasone furoate and vilanterol is approved as inhalation dry powder for the once-daily treatment of asthma in patients 18 years of age and older.

The study outlined in this Written Request is designed to provide evidence of efficacy and safety for use of the fixed-dose combination of fluticasone furoate and vilanterol inhalation powder in children 5 to 17 years of age. Study 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 fluticasone furoate and vilanterol inhalation powder, 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.

[2] 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.

- *Clinical study:*

  A randomized, double-blind, parallel-group, multicenter, 12-week study with a 12-week safety extension, evaluating the efficacy and safety of once-daily fluticasone furoate/vilanterol inhalation powder compared to once-daily fluticasone furoate inhalation powder in patients 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Final protocol must be agreed upon with the Agency.

- *Objective of each study:*

  To demonstrate the efficacy and safety of fluticasone furoate/vilanterol inhalation powder compared with the corresponding dose(s) of fluticasone furoate inhalation powder in children 5 to 17 years of age.

- *Patients to be Studied:*

  - *Age Group in which study will be performed:* Children aged 5 to 17 years (inclusive).

  - *Number of patients to be studied:* The study must enroll a minimum of 850 patients, 5 to 17 years of age inclusive. Of these, a minimum of 650 must be aged 5 to 11 years (at least 160 must be age 5 to < 8 years old) and 220 must be age 12 to 17 years old.

  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:*

  The primary efficacy endpoint for the 5-17 year old population must be the weighted mean FEV_1 (0-4 hours) at Week 12. Secondary variables must include the use of rescue medication and ACQ-5 as well as the incidence of asthma exacerbations over the 24-week treatment period.

  Safety variables must include adverse events, discontinuations due to adverse events, serious adverse events, physical examinations (including oropharyngeal examinations).

- *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.

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 these safety concerns must be performed in the clinical trials.

- *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:* inhalation powder
  - *route of administration:* oral inhalation
  - *Regimen:* once 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.

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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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:*

The study must have a pre-specified, detailed statistical analysis plan appropriate for the study design and outcome measures. The study must be designed to provide at least 90% statistical power to detect a treatment difference of 90 mL in primary endpoint, at a conventional statistical significance level (two-sided α = 0.05). In this study, participants who discontinue study medication should remain in the study and continue with the normal visit schedule and provide all of the expected data unless consent is withdrawn. The main analysis for all efficacy endpoints must evaluate the primary de facto estimand of treatment policy (effectiveness-type estimand) which is defined as: the mean difference between treatment groups for the time point of interest regardless of whether the participant remained on-treatment. This means that for any given endpoint, all available data for a participant will be used including any data that was collected after the participant discontinued study medication. Patients who withdraw consent must be imputed using a method specified in the statistical analysis plan prior to data unblinding.

In order to assess potential impact of missing data, you must conduct a tipping point analysis that varies assumptions about the missing outcomes on the different treatment arms by systematically varying deviations from the benchmark assumption of the primary analysis. The tipping point analysis must be two-dimensional, i.e., should allow assumptions about the missing outcomes for the two treatment arms must vary independently, and should include scenarios

where dropouts on the fluticasone furoate and vilanterol inhalation powder arm have worse outcomes than dropouts on the fluticasone furoate arm. The goal of the tipping point analysis is to identify and discuss the plausibility of the missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect.

The analysis plan must specify an appropriate method to control type I error in the face of multiple key efficacy endpoints.

Safety data will be summarized by descriptive statistics.

- *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 fluticasone furoate/vilanterol 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 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 July 31, 2023. 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
04/06/2020 12:33:33 PM