DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206038

WRITTEN REQUEST

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Attention: Astrid Cornee
Manager, Global Regulatory Affairs

Dear Ms. Cornee:

Reference is made to your September 7, 2017, Proposed Pediatric Study Request for Orkambi (lumacaftor/ivacaftor).

BACKGROUND:

These studies investigate the potential use of lumacaftor/ivacaftor (LUM/IVA) in the treatment of cystic fibrosis in patients 12 months to less than 6 years of age who are homozygous for the *F508del* CFTR mutation.

Cystic fibrosis (CF) is an autosomal recessive disease that affects approximately 70,000 individuals worldwide with approximately half being less than 18 years of age. Almost 50% of CF patients are homozygous for the *F508del* mutation. CF is associated with chronically debilitating morbidities and high premature mortality. There are no approved medications specifically indicated to treat CF patients <6 years of age homozygous for the *F508del* CFTR mutation.

We acknowledge that Vertex Pharmaceuticals has already completed clinical studies which include pediatric patients. These studies have been the basis for approval of lumacaftor/ivacaftor in CF patients homozygous for the *F508del* CFTR mutation ≥ 6 years of age. However, since the study results have already been submitted to the NDA, they cannot be used to support issuance of a Pediatric Written Request for lumacaftor/ivacaftor. These studies include the following:

- Two 24-week safety/efficacy studies in CF patients homozygous for the *F508del* CFTR mutation 12 years and older followed by a 96-week open-label extension study.

- A 24-week pharmacokinetic/safety study in CF patients homozygous for the *F508del* CFTR mutation 6 to 11 years of age.

As CF is a genetic disease that affects infants at or even before the time of birth, clinical studies that support its use in children <24 months are highly desirable. The disease process is the same regardless of age, and the mechanism of action of the drug is expected to be similar between adult and pediatric patients. This allows extrapolation of efficacy. However, proper dose selection and an assessment of safety in children <24 months of age is needed. The studies outlined in this Written Request include (1) a 24-week pharmacokinetic/safety study in CF patients aged 2 through 5 years homozygous for the *F508del* mutation, (2) a 24-week pharmacokinetic/safety study in CF patients aged 12 to <24 months homozygous for the *F508del* mutation and (3) a two-year open-label safety study in CF patients homozygous for the *F508del* mutation who were 12 to <24 months of age when lumacaftor/ivacaftor treatment was initiated.

Efficacy in patients 12 months to less than 6 years old will be supported by extrapolation from the older population where efficacy was demonstrated in double-blind randomized placebo controlled trials.

These studies do not include subjects from birth to less than 12 months of age. Studies to establish safe and effective dosing for this product in this age group are highly impractical given the number of patients in this age group and uncertainties in the ontogeny of the elimination pathways for lumacaftor and ivacaftor along with the drug-drug interaction between the two drugs.

To obtain needed pediatric information on lumacaftor/ivacaftor, 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 studies:*

  Study 1:
  A two-part (A and B) open-label pharmacokinetic (part A) and safety (part B) study in CF patients ages 2 through 5 years who are homozygous for the *F508del* mutation. The pharmacokinetic (PK) portion of the study (A) must establish dosing based on matching PK parameters with the approved dose in the approved age groups. The safety portion of the study (B) must be 24 weeks in length.

  Study 2:
  A two-part (A and B) open-label pharmacokinetic (part A) and safety (part B) study in CF patients ages 12 to 24 months who are homozygous for the *F508del* mutation. The pharmacokinetic (PK) portion of the study (A) must establish dosing based on matching PK

parameters with the approved dose in the approved age groups. The safety portion of the study (B) must be 24 weeks in length.

- The PK portion for the cohort must be completed to inform dosing prior to initiation of the safety portion of the study.

- Older age cohorts in the PK portion of the study must be completed and data reviewed by the Sponsor to confirm exposure per pre-specified parameters to determine dose prior to proceeding to the younger age cohorts in order to ensure safety. Dosing will target exposures observed in adult CF patients treated with the lumacaftor 400/ivacaftor 250 mg BID regimen.

Study 3:
A open-label study to evaluate the safety of long-term treatment with lumacaftor/ivacaftor combination therapy in patients with CF who are homozygous for the *F508del-CFTR* mutation. This study will enroll pediatric patients who are less than 24 months of age at treatment initiation. Patients will be followed for at least 2 years. Study assessments will include ophthalmologic examinations, clinical labs, growth parameters, hospitalizations, exacerbations, and death. This study may include patients from Study 2. Study 3 will be initiated after dosing is confirmed in Study 2.

- *Objective of each study:*

  Study 1: To evaluate the pharmacokinetics, select the dose of lumacaftor/ivacaftor granules, and assess the initial safety of lumacaftor/ivacaftor in CF patients homozygous for *F508del* aged 2 through 5 years of age.

  Study 2: To evaluate the pharmacokinetics, select the dose of lumacaftor/ivacaftor granules, and assess the initial safety of lumacaftor/ivacaftor in CF patients homozygous for *F508del* aged 12 to <24 months of age.

  Study 3: To evaluate the long-term safety of lumacaftor/ivacaftor combination therapy in CF patients homozygous for *F508del* who are less than 24 months of age at treatment initiation.

- *Patients to be Studied:*

  Study 1:
  - *Age group in which study(ies) will be performed*: 2 through 5 years of age

  - *Number of patients to be studied:*
    Study 1, part A: n≥8
    Study 1, part B: n≥40

  Study 2:
  - *Age group in which study(ies) will be performed*: 12 to <24 months of age

- *Number of patients to be studied:*
  Study 2, part A:
  Cohort 1: Patients aged 18 to <24 months (n≥5)
  Cohort 2: Patients aged 12 to <18 months (n≥5)

  Study 2, part B:
  Cohort 1: Patients aged 18 to <24 months (n≥10)
  Cohort 2: Patients aged 12 to <18 months (n≥10)

Study 3:

- *Age group in which study(ies) will be performed*: Patients who were <24 months of age at the time of treatment initiation with lumacaftor/ivacaftor

- *Number of patients to be studied:* ≥50 patients

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:

- *Pharmacokinetic Endpoints:*
  The pharmacokinetic endpoints will include oral clearance (CL/F), area under the concentration versus time curve (AUC). PK sampling must enable estimation of primary PK parameters with reasonable precision.

- *Pharmacokinetic/Pharmacodynamic Endpoints:*
  The pharmacodynamic endpoints will include sweat chloride and may also include other pharmacodynamics endpoints agreed upon with the Agency.

- *Safety Endpoints:*
  Safety outcomes must include physical exam, vital signs, adverse events, ophthalmologic exams, and clinical labs to include transaminases (AST and ALT) and bilirubin. Ophthalmologic examinations must be performed by a qualified physician at baseline prior to initiation of lumacaftor/ivacaftor and every 6 months while in Study 1. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Study 2:

- *Pharmacokinetic Endpoints:*
  The pharmacokinetic endpoints will include oral clearance (CL/F), area under the concentration versus time curve (AUC). PK sampling must enable estimation of primary PK parameters with reasonable precision.

- *Pharmacokinetic/Pharmacodynamic Endpoints:*
  The pharmacodynamic endpoints will include sweat chloride and may also include other pharmacodynamics endpoints agreed upon with the Agency.

- *Safety Endpoints:*
  Safety outcomes must include physical exam, vital signs, adverse events, ophthalmologic exams, and clinical labs to include transaminases (AST and ALT) and bilirubin. Ophthalmologic examinations must be performed by a qualified physician at baseline prior to initiation of lumacaftor/ivacaftor and every 6 months while in Study 2. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

Study 3:

- *Safety Endpoints:*
  Safety outcomes must include physical exam, vital signs, adverse events, ophthalmologic exams, and clinical labs to include transaminases (AST and ALT) and bilirubin. Ophthalmologic examinations must be performed every 6 months, until at least 6 months after the last exposure to lumacaftor/ivacaftor. These examinations must be performed by a qualified physician. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *Known Drug Safety concerns and monitoring:* The following are safety concerns with lumacaftor/ivacaftor therapy: transaminase elevation, respiratory events (dyspnea, discomfort), blood pressure increases and formation of cataract. Monitoring for these events will be performed as listed under Safety Endpoints 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:* granules for oral administration
  - *route of administration:* oral
  - *regimen:* every 12 hours

  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 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 studies are not powered to assess efficacy. Descriptive statistics should be used to describe safety parameters. The pharmacokinetics of lumacaftor/ivacaftor will be characterized using nonlinear mixed effects modeling. The concentration data from the population PK analysis in Study 1 and 2 must be enriched with concentration data from previously conducted lumacaftor/ivacaftor studies in children and adults.

- *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 lumacaftor/ivacaftor 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 1, 2024. 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 Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, MD
Deputy 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/

MARY T THANH HAI
01/04/2018