DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205551

**WRITTEN REQUEST**

ViiV Healthcare Company
Attention: Stephen M. Hyatt, Project Manager
Global Regulatory Affairs
Five Moore Drive
PO BOX 13398
Research Triangle Park, NC 27709

Dear Mr. Hyatt:

Reference is made to your correspondence dated February 21, 2018 requesting the Agency issue a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug and Cosmetic Act (21 USC 355a) for Triumeq, a fixed dose combination product containing abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC).

The study in this Written Request investigate the potential use of ABC/DTG/3TC as part of a fixed dose combination (FDC) drug product, Triumeq, in treating HIV-1 infected pediatric patients weighing 6 kg to less than 40 kg.

**BACKGROUND:**

Global HIV statistics by UNAIDS state that approximately 37 million people were living with HIV in 2015, including 1.8 million children less than 15 years of age.

Effective treatment of HIV infection requires combination therapy with multiple active antiretrovirals. Integrase strand transfer inhibitor (INSTI)-based regimens are among the preferred regimens by the DHHS treatment guidelines for initiating treatment in adult and older pediatric patients with HIV infection. Triumeq may provide an alternative INSTI-based FDC regimen for younger pediatric patients. Triumeq is administered as one pill once daily to provide a complete regimen for the treatment of HIV infection. A single tablet regimen, administered once daily might improve adherence to therapy by reducing the pill-burden and might potentially decrease the risk of drug-resistance due to non- adherence.

The Division of Antiviral Products (DAVP) has determined the course of HIV infection and disease in pediatric patients is sufficiently similar to HIV infection and disease in adults to allow extrapolation of efficacy from the adult clinical trials to pediatric patients. As Triumeq is an antiretroviral FDC product (i.e., directly acts on the virus to prevent replication), pediatric patients with HIV infection are expected to respond similarly to adults treated with Triumeq if they achieve similar drug exposures.

Therefore, efficacy in pediatric patients will be in part supported and extrapolated from the adult trials that evaluated the efficacy of Triumeq, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

A study in pediatric patients weighing less than 6 kg (including neonates), is not included in this Written Request for the following reasons. In patients weighing less than 6 kg, Triumeq is unlikely to be used in a substantial number of patients; studies in pediatrics patients younger than 29 days are impossible or highly impracticable because the number of patients in this age group is too small and geographically dispersed to allow studies.

No studies are requested in pediatric patients 12 years and older or weighing at least 40kg because Triumeq is already indicated for the treatment of HIV infection in this pediatric population.

To obtain needed pediatric information on Triumeq, 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 and the Food and Drug Administration Safety and Innovation Act, that you submit information from the study described below.

- *Nonclinical studies*:

  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:*

  Conduct a study in HIV-infected pediatric subjects weighing at least 6 kg to less than 40 kg who are treatment-naïve or treatment-experienced but INSTI-naïve, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of Triumeq. Subjects must be monitored for a minimum of 24 weeks to assess safety and durability of the antiviral response.

  The dose selection and final protocol must be based on discussions and agreement between the sponsor and the Agency following review of the pediatric PK data and the results of the adult PK and efficacy trials. Weight-based cohort enrollment is recommended.

- *Objectives of the study:*

  The objectives of the study are pharmacokinetics, dose determination, safety and antiviral activity of Triumeq in HIV-1-infected pediatric subjects.

- *Number of subjects to be studied:*

  Triumeq must be studied in an adequate number of pediatric subjects to characterize adverse events across the weight (and age) range with at least 24-week safety data at the recommended dose or higher is required. A minimum of 30 subjects weighing 6 to less than 20 kg (younger than approximately 6 years of age) and a minimum of 30 subjects weighing 20 to less than 40 kg (approximately ages 6 years to <12 years) must be enrolled in the study to evaluate the safety, PK and antiviral activity of Triumeq.

- *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 subjects, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - Pharmacokinetics: Parameters including $C_{max}$, $C_{min}$, $T_{max}$, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution necessary for establishing steady state for all the components of Triumeq (abacavir, dolutegravir, lamivudine).

  - Safety and tolerability: HIV-1-infected pediatric subjects must be followed for a minimum of 24 weeks at the recommended dose or higher to assess the safety of Triumeq; specific safety endpoints must be agreed upon with the Agency in the protocol. In addition, submit plans for collecting long-term safety data for HIV-1-infected pediatric subjects who have received Triumeq.

  - Efficacy: Assessment of changes in plasma HIV RNA levels, including the proportion of subjects with undetectable plasma HIV RNA, and assessment of CD4+ cell counts after a minimum of 24 weeks of treatment.

  - Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving Triumeq, particularly from those who experience loss of virologic response. Conduct HIV-1 proviral DNA resistance testing on baseline samples collected from virologically suppressed subjects, if needed.

- *Known Drug Safety concerns and monitoring:*

  Age appropriate safety outcomes must include adverse events and tolerability. Based on available toxicity information about your product, provide specific safety parameters in your protocol that your pediatric program will monitor. Safety monitoring and data collection must include, but not be limited to:

  1. Hypersensitivity adverse events
  2. Neuropsychiatric adverse events
  3. Effect on humoral and cellular immune system maturity
  4. Development of resistance substitutions in HIV leading to loss of efficacy of HIV therapy
  5. Hepatic toxicity

- *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: Age-appropriate, fixed-dose combination formulation
  - route of administration: Oral
  - regimen: Age-appropriate formulation

  The selected dose(s) for the study must be agreed upon with the Division prior to initiating the necessary safety and antiviral activity pediatric study.

  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 study 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 study 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:*

  Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects are required. The study must include an adequate number of subjects to characterize pharmacokinetics for dose selection. In HIV treatment-naïve and HIV

treatment-experienced (INSTI-naïve) subjects, the study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of abacavir, dolutegravir and lamivudine clearance in the described weight bands. Final selection of sample size for each weight group must take into account all potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for characterization of pharmacokinetics across the intended weight (age) range.

- *Labeling that may result from the study*:

  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 demonstrate that Triumeq 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.

- *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 subjects of ethnic and racial minorities. All pediatric subjects enrolled in the study 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.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: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

- *Timeframe for submitting reports of the study:*

  Reports of the above study must be submitted to the Agency on or before January 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 study 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 study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. 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, 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 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 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 this study. 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 study 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 Andrew Gentles, Regulatory Project Manager, at (240) 402-5708 or the mainline at (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Ed Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

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/s/
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EDWARD M COX
05/16/2018