DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207561

WRITTEN REQUEST – AMENDMENT 1

Gilead Sciences, Inc.
Attention: Alison Blaschke, MBS, RAC
Regulatory Affairs Senior Associate
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Blaschker:

Please refer to your correspondence dated February 20, 2018, requesting changes to FDA's March 14, 2017 Written Request for pediatric studies for GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 14, 2017 remain the same. (Text added is underlined. Text deleted is strikethrough.)

The studies in this Written Request investigate the potential use of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide as part of a fixed dose combination (FDC) drug product, Genvoya, in treating HIV-1 infected pediatric patients weighing at least 14 kilograms (kg) and 2 years to less than 12 years of age.

BACKGROUND:

Therefore, efficacy in pediatric patients ~~between the ages of 2 to less than 12 years old~~ will be in part supported and extrapolated from the adult trials that evaluated the efficacy of Genvoya, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

A study in HIV-infected pediatric patients 2 to 6 years of age and weighing at least 14 kg~~2 to 6 years of age~~ is requested in this Pediatric Written Request for the following reason. At the time of Genvoya approval, the PREA requirement in pediatric patients 29 days up to 6 years was waived because FDA found that Genvoya did not represent a meaningful therapeutic benefit over the existing therapies for those pediatric patients, and it was not likely to be used in a substantial number of pediatric patients in that age group. This waiver was dependent on the availability of the individual drug components within Genvoya to potentially allow for more accurate dosing across the weight-bands of rapidly growing children (e.g., less than 6 years of age). Subsequently, Gilead submitted a request to withdraw NDA 203093 for VITEKTA (elvitegravir), which contains the same active ingredient as one of the components of Genvoya. Because VITEKTA (elvitegravir) will no

longer be available, and because there will be no further pediatric development of VITEKTA (elvitegravir), we are requesting a study to evaluate Genvoya in HIV-infected pediatric patients 2 to 6 years of age and weighing at least 14 kg.~~2 years to less than 6 years of age.~~

A study in pediatric patients younger than 2 years of age or weighing less than 14 kg, including neonates, is not included in this Written Request because alternative 3-drug regimens, including FDC products may be easier to administer compared to a 4-drug FDC regimen, such as Genvoya. Additionally, in patients younger than 2 years of age and weighing less than 14 kg~~29 days to less than 2 years of age~~, Genvoya 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.

Clinical Studies:

Conduct studies in HIV-infected pediatric subjects 2 years of age and older in two cohorts: those weighing 14 to less than 25 kg and those weighing at least 25 kg ~~2 to less than 12 years old~~ who are treatment-naïve, or treatment-experienced but virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of Genvoya. Subjects must be monitored for a minimum of 24 weeks to assess safety and durability of the antiviral response; the durability of response must also be assessed after 48 weeks of therapy.

Number of subjects to be studied:

Genvoya 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. The study in subjects weighing at least 25 kg (ages 6 years to <12 years) must evaluate Genvoya in a minimum of 20 subjects. Similarly, the study in pediatric subjects weighing 14 to less than 25 kg (ages 2 years to <6 years) must evaluate Genvoya in a minimum of 20 subjects.

Drug information:

- dosage form: Age-appropriate fixed dose combination formulation
- route of administration: Oral
- regimen: To be determined by development program ~~Age-appropriate formulation~~

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. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. In HIV treatment-naïve and HIV treatment-experienced 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 elvitegravir, emtricitabine,

and tenofovir alafenamide 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 band~~age range~~.

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 March 14, 2017, as amended by this letter, must be submitted to the Agency on or before March 31, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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 Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at 301-796-0807.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

The studies in this Written Request investigate the potential use of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide as part of a fixed dose combination (FDC) drug product, Genvoya, in treating HIV-1 infected pediatric patients weighing at least 14 kilograms (kg) and 2 years to less than 12 years of age.

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. Genvoya may provide an alternative INSTI-based regimen for younger pediatric patients. Genvoya 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 is believed to improve adherence to therapy by reducing the pill-burden and 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 Genvoya 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 Genvoya 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 Genvoya, and by pharmacokinetic/pharmacodynamic and safety data from pediatric patients.

A study in HIV-infected pediatric patients 2 to 6 years of age and weighing at least 14 kg is requested in this Pediatric Written Request for the following reason. At the time of Genvoya approval, the PREA requirement in pediatric patients 29 days up to 6 years was waived because FDA found that Genvoya did not represent a meaningful therapeutic benefit over the existing therapies for those pediatric patients, and it was not likely to be used in a substantial number of pediatric patients in that age group. This waiver was dependent on the availability of the individual drug components within Genvoya to potentially allow for more accurate dosing across the weight-bands of rapidly growing children (e.g., less than 6 years of age). Subsequently, Gilead submitted a request to withdraw NDA 203093 for VITEKTA (elvitegravir), which contains the same active ingredient as one of the components of Genvoya. Because VITEKTA (elvitegravir) will no longer be available, and because there will be no further pediatric development of VITEKTA (elvitegravir), we are requesting a study to evaluate Genvoya in HIV-infected pediatric patients 2 to 6 years of age and weighing at least 14 kg.

A study in pediatric patients younger than 2 years of age or weighing less than 14 kg, including neonates, is not included in this Written Request because alternative 3-drug regimens, including FDC products may be easier to administer compared to a 4-drug FDC regimen, such as Genvoya. Additionally, in patients younger than 2 years of age and weighing less than 14 kg, Genvoya 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 group is too small and geographically dispersed to allow studies.

No studies are requested in the adolescent population because the indication for Genvoya already includes pediatric patients 12 years of age and older.

To obtain needed pediatric information on Genvoya, 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 studies 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 Studies:*

  Conduct studies in HIV-infected pediatric subjects 2 years of age and older in two cohorts: those weighing 14 to less than 25 kg and those weighing at least 25 kg who are treatment-naïve, or treatment-experienced but virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of Genvoya. Subjects must be monitored for a minimum of 24 weeks to assess safety and durability of the antiviral response; the durability of response must also be assessed after 48 weeks of therapy.

  The dose selection 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.

- *Objective of each study:*

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

- *Number of subjects to be studied:*

  Genvoya 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 required. The study in subjects weighing at least 25 kg (ages

6 years to <12 years) must evaluate Genvoya in a minimum of 20 subjects. Similarly, the study in pediatric subjects weighing 14 to less than 25 kg (ages 2 years to <6 years) must evaluate Genvoya in a minimum of 20 subjects.

- *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 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 Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide).

  - Safety and tolerability: HIV-1-infected pediatric subjects must be followed for safety for a minimum of 24 weeks at the recommended dose or higher; 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 Genvoya.

  - 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 48 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 Genvoya, 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 that your pediatric program will monitor. Safety monitoring and data collection must include, but not be limited to:

  1. Gastrointestinal 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

Additionally, since Genvoya will be co-formulated with TAF, the following need to be monitored:

1. Renal toxicity arising during dosing
2. Possible ocular toxicity (i.e., posterior uveitis)
3. Possible bone toxicity

A Data Monitoring Committee (DMC) may be helpful. S e Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *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: Age-appropriate fixed dose combination formulation
  - route of administration: Oral
  - regimen: To be determined by development program

The selected dose(s) for studies must be agreed upon with the Division prior to initiating the necessary pediatric studies.

Use an age-appropriate formulation in the studies 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:*

  Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects are required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. In HIV treatment-naïve and HIV treatment-experienced 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 elvitegravir, emtricitabine, and tenofovir alafenamide 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 band.

- *Labeling that may result from the studies*:

  You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that Genvoya 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 studies. 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 studies.

- *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 studies 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 studies:*

  Reports of the above studies must be submitted to the Agency on or before March 31, 2021. 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 studies. 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 studies, 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 studies 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 studies 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 and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
06/25/2018