sNDA 207561/S-014: Genvoya
sNDA 208215/S-005: Descovy
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Clinical and Cross-Discipline Team Leader Review

Date	September 10, 2017
From	Melisse Baylor, M.D.
Subject	Clinical Review

Genvoya™

Supplemental NDA #	207561 / Supplement 014
Applicant	Gilead Sciences, Incorporated
Date of Submission	April 3, 2017
PDUFA Goal Date	September 10, 2017
Proprietary Name/ Established (USAN) names	GENVOYA / Fixed Dose Combination of elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF)
Dosage forms / Strength	Oral tablets: elvitegravir (150 mg), cobicistat (150 mg), emtricitabine (200 mg), and tenofovir alafenamide (10 mg)
Proposed indication(s)	Indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg
Recommendation on Regulatory Action	Approval

Descovy™

Supplemental NDA #	208215 / Supplement 005
Applicant	Gilead Sciences, Incorporated
Date of Submission	April 11, 2017
PDUFA Goal Date	September 18, 2017
Proprietary Name/ Established (USAN) names	DESCOVY / Fixed Dose Combination of emtricitabine (FTC) and tenofovir alafenamide (TAF)
Dosage forms / Strength	Oral tablets: emtricitabine (200 mg) and tenofovir alafenamide (25 mg)
Proposed indication(s)	Indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg. Also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg
Recommendation on Regulatory Action	Approval

1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of Genvoya and Descovy use in pediatric patients. The data support extension of the Genvoya indication to include the pediatric population of patients weighing at least 25 kg and extension of the Descovy indication to include patients weighing at least 35 kg OR at least 25 kg and less than 35 kg if the patient is not receiving a protease inhibitor that requires a CYP3A inhibitor.

The application was granted a priority review for several reasons. The data in the application are in response to post-marketing requirements (PMR) issued under the Pediatric Research Equity Act (PREA) for both Genvoya and Descovy. In addition, the application for Genvoya allows for the use of a fixed dose combination tablet taken once daily in the pediatric population, which will provide the first single tablet regimen for the HIV-1 infected patient population weighing at least 25 kg.

2. Background

This supplemental NDA contains the results of a single study, GS-US-292-0106, a pharmacokinetic, safety, and antiviral activity study of Genvoya in adolescents and pediatric patients. Data from this study were submitted to support the use of both Genvoya and Descovy in pediatric patients. Both Genvoya and Descovy are fixed dose combination tablets. While Genvoya contains elvitegravir (150 mg), cobicistat (150 mg), emtricitabine (200 mg), and tenofovir alafenamide (TAF) (10 mg), Descovy contains emtricitabine (200 mg), and tenofovir alafenamide (25 mg) only. The difference in the TAF dose between the two products is a result of the pharmacokinetic boosting effect of cobicistat; coadministration of cobicistat with 10 mg TAF results in the same tenofovir exposure as administration of 25 mg TAF without a CYP3A inhibitor. Descovy was approved for use in adults and adolescents based on the demonstration of bioequivalence and bioavailability of Descovy and Genvoya and on the pharmacokinetic bridging of the corresponding components of Descovy to the respective components of Genvoya. The use of data from study GS-US-292-0106 to support approval in pediatric patients is based on past evidence of comparable pharmacokinetic data between Descovy and Genvoya with extrapolation of safety and efficacy from the study of Genvoya.

2.1 Genvoya

Genvoya (a fixed dose combination tablet of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide), was granted Traditional Approval on November 5, 2015. Genvoya was the fourth single tablet, once daily regimen approved for the treatment of HIV-1 infection. The approval in HIV treatment-naïve adult patients was based on data from two Phase 3 trials (GS-US-292-0104 and GS-US-292-0111). These trials were randomized, double-blinded studies, in which the active comparator was Stribild®; Stribild is a FDA-approved fixed dose combination tablet consisting of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate. Both tenofovir alafenamide and tenofovir disoproxil fumarate are prodrugs of the active drug, tenofovir. The trial designs for GS-US-292-0104 and GS-US-292-0111 were identical. Treatment-naïve, HIV-1 infected adults were randomized in a 1:1 ratio to receive either Genvoya or Stribild for 48 weeks. The percentage of subjects with HIV-1 RNA levels <50 copies/mL at Week 48 in GS-US-292-0104 was 93.1% in the Genvoya arm and 92.4% in the Stribild arm (95% confidence interval of -2.6%, 4.5%); the percentage of subjects with HIV-1 RNA levels <50 copies/mL at Week 48 in GS-US-292-0111 was 91.6% in the Genvoya arm and 88.5% in the Stribild arm (95% confidence interval of -1.0%, 7.1%). In combined data from the

two studies, the mean increase in CD4 lymphocyte cells at a later time point in the study (Week 114) was 326 cells/μL in the Genvoya arm and 305 cells/μL in the Stribild arm. These efficacy data supported an indication for treatment of treatment-naïve adults with Genvoya.

The approval of Genvoya to replace the current antiretroviral (ARV) regimen in adult patients who are virologically suppressed (e.g., a switch study design) was based on data from one Phase 3 trial (GS-US-292-0109). In this trial, HIV-1 infected adults who were virologically-suppressed on their current ARV regimen were randomized in a 2:1 ratio to switch to Genvoya or remain on their current regimen. After 48 weeks of treatment, 96% of subjects in the Genvoya arm had HIV-1 RNA levels < 50 copies/mL compared to 93% in the control arm. The mean change in CD4 cell count from baseline to Week 48 was +33 cell/μL in the Genvoya arm and +26 cells/μL in the control arm.

Genvoya is currently approved for use in HIV-1 infected adolescent patients from 12 to <18 years of age weighing at least 35 kg. This approval was based on the results of Cohort 1 of Study GS-US-292-0106, which is an ongoing, open-label, non-comparative, two-part study of the pharmacokinetics (PK), safety, and antiviral activity of Genvoya in adolescents and pediatric patients. Treatment-naïve adolescents from 12 through 17 years of age were enrolled in Cohort 1 of the study. In Part A of Cohort 1, pharmacokinetics of Genvoya were evaluated and the dose of Genvoya was confirmed. In Part B of the study, subjects were treated through 48 weeks. Safety was evaluated in both cohorts. After 24 weeks of Genvoya, HIV RNA levels were less than 50 copies/ml in 21 of 23 subjects (91.3%). The mean change in CD4 cell count was +191 cells/μL. The results for Cohort 2 of this study, which was conducted in subjects 6 to <12 years of age, were submitted in this supplemental NDA.

Currently available HIV treatment includes six different antiretroviral drug classes and at least 25 individual antiretroviral drugs, not including fixed drug combinations. The drug classes include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors (INSTIs). Most approved ARVs have dosing recommendations in at least one subset of the pediatric age range.

While there are approved ARVs in multiple classes available for the treatment of HIV infection in children, there continue to be challenges. For example, poor adherence, and short and long term toxicities may contribute to the development of drug resistance and failed therapy. As a result, there is a need for continuous development of new ARVs for treatment of HIV infection. There are currently six single-tablet, once-daily regimens available for the treatment of HIV infection: Genvoya, Atripla®, Complera®, Odefsey®, Triumeq®, and Stribild. However, none of these antiretrovirals are currently approved for pediatric patients less than 12 years of age. The availability of Genvoya allows once daily dosing and offers patient convenience and the potential for increased compliance in pediatric patients.

This pediatric supplement is in response to the outstanding PREA PMR:

> PMR #2971-1: Conduct your deferred pediatric study in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety, tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination. At least some of the safety data must be derived from dosing as the GENVOYA fixed dose combination.

In addition, this application is a partial response to a Written Request for Genvoya.

2.2 Descovy

Descovy was granted Traditional Approval on April 4, 2016. Descovy is a fixed dose combination of emtricitabine and tenofovir alafenamide, a nucleoside reverse transcriptase inhibitor and a nucleotide reverse transcriptase inhibitor, and is not a complete regimen for treatment of HIV-1; Descovy must be combined with a third drug to form a complete regimen for HIV-1 infection.

The approval of Descovy was based on the results of two Phase 1 pharmacokinetic studies that demonstrated the bioequivalence of emtricitabine and TAF in Descovy to their corresponding components in Genvoya. The efficacy assessment of Descovy was based upon the demonstration of bioequivalence to Genvoya; therefore, no efficacy studies of Descovy were conducted. See the discussion of clinical trials conducted to support the efficacy of Genvoya in Section 2.1 of this review and the Descovy NDA. In addition, because of the demonstration of bioequivalence for emtricitabine and TAF in Descovy to those two components of Genvoya, the results of the pediatric study of Genvoya will be used to support the safety and antiviral activity of Descovy.

This pediatric supplement is a partial response to the outstanding PREA PMR:

> PMR #3041-2: Conduct your deferred pediatric study in HIV-infected, virologically suppressed patients 6 years to less than 12 years switching from other nucleoside reverse transcriptase inhibitors (NRTIs) to assess the pharmacokinetics, safety, tolerability, and antiviral activity of age-appropriate DESCOVY tablets in combination with an approved third antiretroviral drug. Study participants should be monitored for 48 to 96 weeks to assess safety and durability of antiviral response.

2.3 Study Conduct

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The Division did not consult the Office of Scientific Investigations for inspection of the clinical trial sites, but bioanalytical inspections were requested for validation of the pharmacokinetic data, which serve as pivotal data for the approvability of these applications. The Division of New Drug Bioequivalence Evaluation recommended accepting the data without an on-site inspection because the site was recently inspected with a satisfactory outcome.

The applicant also submitted financial information pertinent to the application. There were 12 principal investigators and 48 sub-investigators; none were employees of Gilead Sciences. None of the investigators received compensation where the value could have influenced the outcome of the study, none received payments greater than $25,000, none held proprietary interested in the study drug, and none held significant equity interest in Gilead Sciences. Therefore, the conduct of this trial complied with the regulations as defined in 21 CFR 54.4(a)(3)(i), 54.2(a). Please see the Clinical Investigator Financial Disclosure Review Template in Section 16 of this review.

3. CMC

A new formulation was not developed for use in pediatric patients. As a result, no new product information regarding drug substance or manufacturing was submitted. Please refer to the original reviews of NDA 207561 and 208215 for additional information on chemistry and manufacturing.

4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original review of NDA 207561 for details.

5. Clinical Microbiology

Please see the original NDA review for a detailed assessment of the clinical microbiology data.

Of the 23 adolescent subjects in Trial GS-US-292-0106, the only trial in this sNDA, all 23 achieved virologic suppression. Therefore, resistance to the individual components of Genvoya (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) could not be assessed.

6. Clinical Pharmacology / Biopharmaceutics

Please refer to the USPI and reviews from the original NDA for details of adult pharmacokinetics (PK). Please see Dr. Sampson's Clinical Pharmacology review of this application for additional information regarding the pediatric PK results summarized below.

Intensive pharmacokinetic evaluations were performed at Week 4. The plasma levels of each of the four components of Genvoya, elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF), and of the major metabolite of TAF, tenofovir (TFV), were analyzed to characterize their pharmacokinetics in this pediatric population. The PK parameters for EVG, COBI, and FTC were compared to historical adult controls from GS-US-292-0102, a Phase 2 randomized PK, safety, and antiviral activity trial of Genvoya in both treatment-naïve subjects and subjects who switched from a stable ARV regimen to Genvoya. The PK parameters for TAF and TFV were compared to population PK modeling in Genvoya-treated adults in the two pivotal trials of Genvoya, GS-US-292-0104 and GS-US-292-0111. Each PK parameter in pediatrics was compared to adult parameters and a geometric least-square mean ratio and a corresponding 90% confidence interval (CI) were constructed. The equivalency boundary was 70% to 140%.

The PK results and geometric least-square mean ratios for each of the components of Genvoya are shown in the following four tables.

Table 1: Elvitegravir Pharmacokinetic Parameters and Geometric Least-Square Means (GLSM) Ratios Comparing Pediatric to Historical Adult Controls

PK Parameter	Mean Value	GLSM Ratio (90% CI*)
AUC_{tau} (h·ng/mL)	33,813.9	134.05 (103.86, 173.0)
C_{max} (ng/mL)	3,055.2	141.29 (115.31, 173.12)
C_{tau} (ng/mL)	370.0	85.51 (55.01, 132.92)

*CI=confidence interval

Source: Clinical Study Report GS-US-292-0106: Tables 10.1 and 10.2, pages 76-77.

As shown in Table 1, the upper bound 90% CI for the ratio of pediatric to adult PK values for AUC_{tau} and C_{max} were higher than the 140% boundary. Since there is no dose-related safety

concern with EVG, this increased exposure should not be clinically significant. The lower bound 90% CI for C_{tau} was less than the predefined 70% boundary; however, the sponsor notes that it is still more than 8-fold higher than the IC_{95} for the wild-type virus.

Table 2: Cobicistat Pharmacokinetic Parameters and Geometric Least-Square Means (GLSM) Ratios Comparing Pediatric to Historical Adult Controls

PK Parameter	Mean Value	GLSM Ratio (90% CI*)
AUC_{tau} (h·ng/mL)	15,890.7	157.71 (125.79, 197.73)
C_{max} (ng/mL)	2,079.4	127.01, (97.64, 165.21)
C_{tau} (ng/mL)	96.0	171.21 (94.71, 309.51)

*CI=confidence interval
Source: Clinical Study Report GS-US-292-0106: Tables 10-9 and 10-10, page 80.

As shown in Table 2, the upper bound 90% CI for the ratio of pediatric to adult PK values for all three PK parameters were higher than the 140% boundary. Since there is no dose-related safety concern with COBI, this increased exposure should not be clinically significant.

Table 3: Emtricitabine Pharmacokinetic Parameters and Geometric Least-Square Means (GLSM) Ratios Comparing Pediatric to Historical Adult Controls

PK Parameter	Mean Value	GLSM Ratio (90% CI*)
AUC_{tau} (h·ng/mL)	20,629.2	175.03 (159.57, 191.98)
C_{max} (ng/mL)	3,397.4	163.55 (145.11, 184.34)
C_{tau} (ng/mL)	114.9	125.42 (107.40, 146.47)

*CI=confidence interval
Source: Clinical Study Report GS-US-292-0106: Tables 10-12 and 10-13, pages 81-82.

As shown in Table 3, the upper bound 90% CI for the ratio of pediatric to adult PK values for all three PK parameters were higher than the 140% boundary; however, C_{tau} was only slightly over the boundary. Since there is no dose-related safety concern with FTC, this increased exposure should also not be considered clinically significant.

Table 4: Tenofovir Alafenamide (TAF) and Tenofovir (TFV) Pharmacokinetic Parameters and Geometric Least-Square Means (GLSM) Ratios Comparing Pediatric to Adult Controls from Population PK Modeling

PK Parameter	TAF Mean Value	TAF GLSM Ratio (90% CI*)	TFV Mean Value	TFV GLSM Ratio (90% CI*)
AUC_{tau} (h·ng/mL)	332.9	170.66 (146.5, 198.8)	440.2	152.21 (142.3,162.8)
C_{max} (ng/mL)	313.3	181.61 (146.4, 225.3)	26.1	172.99 (161.1,185.8)
C_{tau} (ng/mL)	9.6	NP#	15.1	143.25 (132.3,155.1)

*CI=confidence interval
#NP=not provided
Source: Clinical Study Report GS-US-292-0106: Table 8-5, page 71.

As shown in Table 4, the upper bound 90% confidence interval for the ratio of all of the PK parameters in pediatric subjects compared to adult controls was higher than the 140% boundary for AUC_{tau} and C_{max} for tenofovir and the prodrug tenofovir alafenamide. The upper bound 90% CI for C_{tau} was not provided for TAF but was also higher than the 140% boundary for tenofovir.

Although there are dose-related safety issues associated with tenofovir, these PK exposures are considerably lower than those in pharmacokinetic studies of tenofovir disoproxil fumarate. Therefore, these exposures are clinically acceptable.

In summary, the majority of PK exposure parameters were higher than those observed in adult controls. However, the higher exposures of EVG, COBI, and FTC are acceptable, because there are no dose-related safety concerns with these drugs. Although there are safety concerns with high doses of tenofovir, the tenofovir exposures are considerably lower than levels observed after administration of other tenofovir prodrugs. Therefore, the conclusion is that a single tablet of Genvoya administered daily provides acceptable exposures to its four components in pediatric patients weighing at least 25 kg. Unlike Genvoya, which contains cobicistat, Descovy does not contain a pharmacokinetic enhancer, and therefore contains a higher dose of TAF than Genvoya. Prior studies have shown that protease inhibitors boosted with ritonavir or cobicistat can affect TAF exposures differently than cobicistat alone (please refer to the original Descovy NDA reviews for additional details). Therefore, the pharmacokinetic data support extending the indication for Descovy to patients weighing at least 25 kg if they are not receiving a protease inhibitor with a CY3A inhibitor as part of their ARV regimen. Additional data are required to approve Descovy administered with boosted protease inhibitors for children weighing 25 to 35 kg.

7. Clinical / Statistical – Efficacy

As stated previously, the sNDAs for Genvoya and for Descovy were submitted to fulfill (Genvoya) and partially fulfill (Descovy) outstanding PREA PMRs which required pharmacokinetic, safety, and antiviral activity data in pediatric patients from 6 to less than 12 years of age. While the Descovy PREA PMR requires safety and antiviral activity data for 48 to 96 weeks, the Genvoya PREA PMR does not specify a follow-up period. The clinical trial report focused on the 24 week safety and efficacy analyses. Therefore, the efficacy section of this review summarizes the Week 24 efficacy results for Trial GS-US-292-0106, which is ongoing. Post Week 24 efficacy analyses were not presented by the applicant in the clinical trial report and were not required for approval or labeling. As a result, efficacy data through Week 24 are presented in labeling. In addition, 24-week safety data were submitted to fulfill (Genvoya) and partially fulfill the PREA PMR (Descovy), and the safety section focuses on the Week 24 safety results. Information requests regarding post-24 week safety and efficacy results were communicated to the sponsor, and a limited discussion of 48-week data is included in this review.

Though cross-trial comparisons to the results from the adult trials should be done with caution, the general principal of comparing effectiveness of an ARV drug in children to adults is supported, as further discussed below.

The extrapolation of efficacy for antiretroviral drugs like the components of Genvoya and Descovy is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects [21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c]. DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease, noting that the routes of transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age, in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two parameters, HIV RNA viral load and CD4 count. Antiretroviral drugs including NRTIs, NNRTIs, PIs, and INSTIs are shown to lower HIV RNA, improve CD4 counts (or percentages) and improve general clinical outcome in adult and pediatric subjects. Treatment recommendations are very similar across all age groups [see US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, available at http://aidsinfo.nih.gov/guidelines].

Overview of Trial Design

Trial GS-US-292-0106 is the pivotal pediatric trial evaluating the use of Genvoya. Genvoya was administered orally as a fixed dose combination tablet containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (the adult formulation which is currently marketed). Adolescent subjects from 12 through 17 years of age were enrolled into Cohort 1 of the trial, and the results of Cohort 1 were included in the original NDA submission for Genvoya. Twenty-three subjects were enrolled into Cohort 2 of the trial for intensive PK assessment which allowed for confirmation of the appropriate dose of Genvoya and assessment of the safety, tolerability, and antiviral activity of Genvoya. An additional cohort of subjects ages 6 to < 12 years is enrolling, but data from these subjects were not included in this submission. Hence, this review will focus on the 23 subjects who underwent intensive PK sampling and who have complete data through Week 24.

The primary objectives were to evaluate the PK profile of EVG and TAF and to determine the safety and tolerability of Genvoya through Week 24 in HIV-1 infected children from 6 to less than 12 years of age weighing at least 25 kg. The secondary objectives were to evaluate the antiviral activity of switching to Genvoya in virologically suppressed HIV-1 infected children, to evaluate the PK profile of COBI, FTC, and tenofovir, and to evaluate the safety and tolerability of Genvoya through Week 48. See the Clinical Pharmacology section of this review for a discussion of the pharmacokinetic results of the study.

The trial enrolled treatment-experienced children from 6 to <12 years of age who weighed at least 25 kg. Subjects were infected with HIV-1 and virologically suppressed on their current ARV regimen (defined as a HIV RNA viral load < 50 copies/mL). Subjects had to have been receiving their current regimen for at least 180 consecutive days; changes in the antiretroviral regimen due to reasons other than virologic failure were allowed. Patients with a history of resistance to any of the components of Genvoya were not allowed to participate in the trial. Subjects had to have a baseline CD4 cell count greater than 100 cells/μL. Patients were excluded from participation in the trial for decreased renal function (estimated glomerular filtration rate <90 mL/min/1.73m^2) or for positive serology for Hepatitis B or C virus.

Genvoya dosing was one tablet administered once daily, the same dosage recommended for adolescents and adults.

Subjects were followed for safety and tolerability as well as efficacy for 48 weeks with an option to continue until the subject reaches 18 years of age and Genvoya is commercially available for adults in the country in which the subject is enrolled, or until Genvoya is commercially available for pediatric patients in the country in which the subject is enrolled. Efficacy was assessed at Weeks 24 and 48 by evaluation of immunologic changes and changes in HIV RNA viral load. Resistance information was to be evaluated in subjects with loss of virologic response (HIV RNA ≥ 400 copies/mL).

Trial GS-US-292-0106 was reviewed for efficacy, safety and tolerability, and pharmacokinetics. Subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results were reviewed using JMP Statistical software.

Disposition
A total of 26 subjects were screened for study participation, and 23 subjects received at least one dose of study drug (Genvoya). Of the 23 subjects, all 23 (100%) were ongoing at the Week 24 analysis cut-off date for the Clinical Study Report. There were no premature discontinuations.

Demographics and Baseline Characteristics
The Full Analysis Set included all 23 subjects. The majority of subjects were female (61%) and Black/African American (78%). The mean age of subjects was 10.0 years. The mean weight was 31.6 kg with a weight range of 25.2 to 58.2 kg. The median weight was 30.5 kg with a first quartile of 27.5 kg and a third quartile of 33.0; therefore, an acceptable range of weights was studied.

As specified in the study protocol, all 23 subjects had baseline HIV RNA <50 copies/mL. The mean CD4 cell count at baseline was 966 cells/μL; the median CD4 count was 969 cells/μL, and the CD4 cell count range was 603 to 1421 cells/μL. All 23 subjects acquired HIV via mother-to-child transmission, and the mean number of years since diagnosis was 8.8. The HIV disease status for all 23 subjects was asymptomatic.

Subjects were switched from a stable ARV regimen to Genvoya. The antiretroviral medication received prior to the first dose of Genvoya is shown in the following table.

Table 5: Antiretroviral Medication Received Prior to Switching to Genvoya

Antiretroviral Class and Medication	Number of Subjects
Nucleoside reverse transcriptase inhibitors	23 (100%)
Lamivudine	19 (83%)
Abacavir	14 (61%)
Zidovudine	12 (52%)
Emtricitabine	4 (17%)
Tenofovir DF	2 (8.7%)
Nonnucleoside reverse transcriptase inhibitors	11 (48%)
Efavirenz	7 (30%)
Nevirapine	4 (17%)
Integrase inhibitors	2 (8.7%)
Raltegravir	2 (8.7%)
Protease inhibitors	5 (22%)
Lopinavir/ritonavir	4 (17%)
Atazanavir	1 (4.3%)
Ritonavir	1 (4.3%)

Source: Clinical Study Report GS-US-292-0106: Table 8-5, page 71.

As shown in Table 5, all subjects had been receiving an ARV regimen containing a nucleoside reverse transcriptase inhibitor; of these two had received tenofovir disoproxil fumarate prior to switching to Genvoya, which contains the alafenamide formulation of tenofovir. Over half of subjects had received lamivudine (83%), abacavir (61%), or zidovudine (52%). Thirty percent of

subjects had received the nonnucleoside reverse transcriptase inhibitor, efavirenz; no other ARV was being used in more than 20% of subjects.

Efficacy Results at Week 24

There was no primary efficacy endpoint for this trial; however, there were three efficacy endpoints:

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm,
- The change from baseline in CD4 cell count (cells/μL) and percentage at Weeks 24 and 48, and
- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 (missing=failure and missing=excluded methods).

Genvoya demonstrated antiviral activity over the 24 week trial period. The proportion of subjects with plasma viral load <50 copies/mL at Week 24 was 100%. There were no missing data at Week 24 therefore, the endpoint using missing as failure or excluded was not performed. These results are consistent with antiviral activity results in the pivotal trial, GS-US-292-0109, in which HIV-infected adults were switched from their current regimen to Genvoya. In GS-US-292-0109, the percentage of adult subjects with HIV RNA <50 copies/mL at Week 48 was 96%.

The CD4 cell count was measured at screening and baseline and at Weeks 2, 4, 8, 12, 16, and 24. The mean baseline CD4 cell count was 966 cells/μL, and the mean change in CD4 count at Week 24 was -150 cells/μL. The mean CD4 percentage at baseline was 39.6%; the mean change in CD4 percentage at Week 24 was -1.5%. The mean change in CD4 cell count and percentage at each time point after Genvoya was started is shown in the following table.

Table 6: Mean Change in CD4 Cell Count and Percentage at Each On-Treatment Time Point up to Week 24

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
CD4 Count (cells/μL)	-162	-125	-134	-162	-133	-150
CD4 Percentage	+0.5	-0.1	+0.3	-0.8	-0.5	-1.5

Source: Clinical Study Report GS-US-292-0106: Tables 12-13, pages 138-139.

As shown in Table 6, the mean change in CD4 cell count decreased at Week 2 and remained decreased throughout the 24 week study period. The mean change in CD4 percentage was positive at Weeks 2 and 8 and was only -1.5% from baseline at Week 24. The mean change in CD4 cell counts at Week 48 in Trial GS-US-292-0109, in which virologically suppressed HIV-infected adults were randomized to switch from their current ARV regimen to either Genvoya or Stribild was +33 cells/μL in the Genvoya arm and +26 in the Stribild arm. The lack of a large increase in CD4 counts in subjects who have HIV RNA <50 copies/mL, who switch from one ARV regimen to another, and who remain virologically suppressed, is consistent with a stable HIV disease course. In the adolescent cohort (Cohort 1 of GS-US-292-0106), the baseline CD4 cell count was 471 cells/μL and the mean increase in the CD4 count at Week 24 was +224 cells/μL. However, all of the adolescent subjects were treatment-naïve with detectable HIV RNA at baseline.

The applicant provided CD4 cell count, CD4 percentage, and percentage with HIV RNA < 50 copies/mL at time points from Week 24 to Week 48 in GS-US-292-0106. These results are shown in the following table.

Table 7: Mean Change in CD4 Cell Count and Percentage at Each On-Treatment Time Point from Week 24 to Week 48

	Week 24	Week 32	Week 40	Week 48
CD4 Count (cells/μL)	-150	-88	-31	-90
CD4 Percentage	-1.5	-1.1	-0.9	-1.3

Source: NDA 207561, Sequence Number 0129, Response to FDA Information Request. Table 1, page 4.

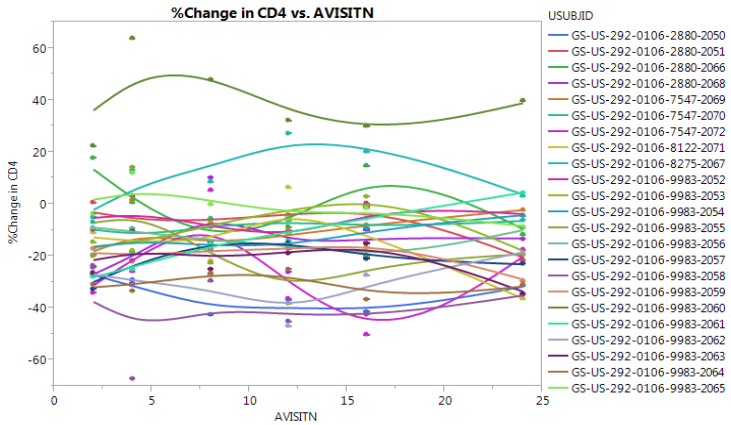
As shown in Table 7, the decrease in CD4 count improved over time and was -90 cells/μL at Week 48. The mean change in CD4 percentage was similar at Week 24 (-1.5%) and Week 48 (-1.3%). All 23 subjects had HIV RNA < 50 copies/mL at Week 48.

Multiple reasons for the decrease in CD4 cell count were explored. The decrease in CD4 cell counts was not related to a decrease in overall white blood cell count or the absolute lymphocyte count. The white blood cell count was 4.64 x 10^3/dL at baseline and 4.39 at Week 24. The absolute lymphocyte count was 2.23 at baseline and 1.99 at Week 24. Both the overall white blood cell count and the absolute lymphocyte count were slightly decreased at Week 24 but the decrease does not explain the large decrease in CD4 cell counts.

The mean CD4 cell count at screening (956.8 cells/μL) was similar to the mean CD4 count at baseline; therefore, the decrease in CD4 cell count was not related to statistical chance with an abnormally high baseline CD4 cell count.

The possibility that the decrease in CD4 count was due to a few outliers with large decreases in CD4 counts was explored; however, as shown in the following figure of percent change in CD4 shows, there results were not driven by outliers.

Figure 1: Change in CD4 Percentage from Baseline to Week 24 by Individual Study Subject



Source: Clinical Study Report GS-US-292-0106, figure constructed from laboratory test results (LB) dataset.

In Figure 1, each line represents the CD4 cell percentage for an individual subject. The x axis is time in weeks and the y axis is the percent change. As shown in Figure 1, the results are clustered below 0 and were not driven by outliers.

The decrease in CD4 count did not correlate with AUC of any of the four drug components of Genvoya.

The applicant was asked to provide any available information on decreased CD4 cell count after treatment with Genvoya or any of its components. Preliminary data from an additional cohort of 25 subjects 6 to < 12 years of age (not included in the current efficacy supplement because they were not enrolled until the PK results of the first cohort were available and have not completed 24 weeks of treatment) were provided. The mean baseline CD4 cell count was 946 cells/μL, the mean CD4 cell count at Week 2 was 946 cells/μL, and the mean cell count at Week 8 was 889 cells/μL. The mean decrease in CD4 cell count was -82 at Week 2 and -16 at Week 8.

The sponsor also provided a brief summary through Week 48 of the results of one study in adolescents, GS-US-216-0128. In this Phase 2/3, open-label, pharmacokinetic, safety, and antiviral activity trial, HIV-1 adolescents who were virologically suppressed on an ARV regimen using ritonavir as a pharmacokinetic enhancer were switched from ritonavir to cobicistat. The mean baseline CD4 cell count was 989 cells/μL and the mean change in CD4 cell count at Week 48 was -144. Nineteen of the 20 subjects in the trial had HIV RNA < 50 copies/mL at Week 48.

The sponsor provided the results of an additional study in which 60 virologically-suppressed, HIV-infected adolescents were switched from their current ARV regimen to Genvoya. In this trial, the mean baseline CD4 cell count was 757 cells/μL and the mean CD4 cell count decreased to 717 cells/μL at Week 72. Five subjects with baseline CD4 cell counts <500 cells/μL had a mean increase in CD4 cell count at Week 2 of 29 cells/μL;, the standard deviation (142) for this increase was wide, therefore, the results of only five subjects is difficult to interpret.

The reason for the decrease in CD4 cell counts after the switch to Genvoya is unclear. In the opinion of this reviewer, the most likely explanation is twofold. First, the mean baseline CD4 count was high (966 cells/μL) and fluctuations such as -150 cells/μL appear large but are actually only a 1.5% change in the CD4 percentage. Second, when subjects who are virologically suppressed are switched to a new ARV regimen and remain virologically suppressed, there is unlikely to be a substantial change in CD cell count. In the trial of adults who were switched to Genvoya (GS-US-292-0109), the mean increase in CD4 cell count at Week 48 was only +33 cells/μL. In the cobicistat trial (GS-US-216-0128), in which adolescents were switched from ritonavir to cobicistat, the mean baseline CD4 cell count was 989 cells/μL and the mean change in CD4 cell count at Week 12 was -153. In this trial with a similar design and with a high mean baseline CD4 cell count, the CD4 cell count also decreased on the new regimen. The applicant attributes the decrease in CD4 cell count to normal fluctuations in CD4 cell counts that are observed in HIV-infected patients, and more commonly in HIV-infected pediatric patients.

The applicant provided results for CD4 cell counts from an additional three trials in virologically suppressed, HIV-infected adults who were switched to Genvoya. The applicant provided the results for subjects with baseline CD4 cell counts <500 cells/μL compared to those with baseline CD4 cell counts ≥ 500 cells/μL to evaluate the risk of a decrease in CD4 cell counts in patients with a low CD4 cell count at baseline. The results are shown in Table 8.

Table 8: Mean Change in CD4 Cell Counts by Baseline CD4 Count in Trials in which Virologically-Suppressed Adults were Switched to Genvoya

	CD4 Count at Baseline (cells/μL)			
	Genvoya		Control*	
	<500	≥500	<500	≥500
GS-US-292-0119^ Mean Change at Week 48	N=39 +34 cells/μL	N=39 -17 cells/μL	N=22 +53 cells/μL	N=24 +28 cells/μL
GS-US-292-1823 Mean Change at Week 24	N=43 +11 cells/μL	N=140 -40 cells/μL	N=87 +20 cells/μL	N=71 -13 cells/μL
GS-US-292-1826 Mean Change at Week 48	N=30 +57 cells/μL	N=79 +60 cells/μL	N=16 +16 cells/μL	N=39 -69 cells/μL

*Controls remained on the stable regimen
^Results from Cohort 1, a small PK cohort of this study are not included
Source: NDA 207561, Sequence 317, Information Request.

The applicant concluded that based on the data in Table 8 patients with a low baseline CD4 count are not at increased risk of immunosuppression. In the opinion of the clinical review team, the data are limited, but the information in Table 8 suggest that subjects with a low baseline CD4 cell count will not be at an increased risk of immunosuppression after switching to Genvoya.

In conclusion, the reason for the decrease in CD4 cell count is unclear. However, no pediatric subjects had CD4 cell counts less than 500 cells/μL at any time during the GS-US-292-0106, and no illnesses consistent with immunosuppression were reported. Therefore, the decrease in CD4 cell count did not appear to be clinically significant. However, the lack of data in pediatric patients and the risk of a decrease in CD4 cell count that results in immunocompromised cannot be ruled out; therefore, the information will be included in the package insert.

Efficacy Summary and Conclusions
The antiviral activity of a single tablet dose of oral Genvoya administered once daily in the treatment of treatment-experienced HIV-1 infected pediatric patients from 6 to <18 years of age who were switched from a previous regimen to Genvoya was demonstrated in this single arm, uncontrolled trial. All 23 subjects had HIV RNA levels < 50 copies mL at baseline prior to switching to Genvoya and at Week 24 on Genvoya. However, there was a decrease in the mean CD4 cell count of -150 cells/μL at Week 24. This may have been related to the high baseline mean CD4 cell count and the switch design of the study. This information will be included in the package insert. The antiviral response rate is consistent with the antiviral response observed in the trial of treatment-experienced adults who were switched to Genvoya, and the lack of a robust increase in CD4 cell counts on Genvoya was also observed in the adult switch studies.

In summary, the exposure data from the intensive PK analyses support the dosing of Genvoya in patients weighing at least 25 kg and the efficacy outcomes as measured by HIV RNA in Trial GS-US-292-0106 are consistent with results observed during trials of treatment-experienced adults. Therefore, these results support the antiviral activity of Genvoya in treatment experienced, virologically-suppressed, HIV-infected pediatric patients weighing at least 25 kg who switch from a stable antiretroviral regimen to Genvoya. These data also support the use of Descovy, in combination with a third ARV that is not a boosted protease inhibitor, for children weighing at least 25 kg but less than 35 kg. Previous PK data support the use of efficacy data from Genvoya to support the efficacy of Descovy. However, since Descovy is a two-drug fixed combination tablet, it must be used with a third antiretroviral agent.

8. Safety

The data submitted support the safety and tolerability of Genvoya in HIV-infected pediatric patients weighing at least 25 kg. The applicant has submitted safety data from 23 subjects from 6 to <12 years of age who received at least one dose of Genvoya in Trial GS-US-292-0106. The duration of follow-up was 24 weeks for all 23 subjects. The types of adverse events observed were similar to conditions or illnesses commonly observed during childhood and with the types of AEs observed in HIV-infected, treatment-experienced children and adults. The study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings.

Duration of Treatment

Subjects enrolled in Trial GS-US-292-0106 are to be followed for at least 48 weeks. The Clinical Study Report summarized the safety data for the first 24 weeks. A 60-Day Safety Update was submitted on June 20, 2017. At the time of the Safety Update, all subjects in GS-US-292-0106 had reached their Week 48 visit.

Deaths and Other SAEs

There were no deaths up to Week 48. There were no serious adverse events.

Discontinuations due to Adverse Events

There were no discontinuations due to adverse events.

Adverse Events of Interest

Based on adverse events observed in animal toxicity studies and previous clinical use of tenofovir prodrugs, adverse events of interest were evaluated regardless of AE causality: the AEs of interest were renal toxicity and bone mineral density.

Renal Toxicity

The Genvoya package insert includes new onset or worsening renal impairment as a Warning and Precaution. One of the two primary target organs in chronic toxicity studies of dogs and rats was the kidney. Serous renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) has been reported with clinical use of tenofovir prodrugs. Although the renal toxicity is primarily related to the tenofovir component of Genvoya, cobicistat is associated with an increase in serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration. Serious adverse events regarding renal function and discontinuations due to adverse events of the renal organ system have been reported in less than 1% of Genvoya trials of adults and adolescents with baseline eGFRs greater than 50 mL per minute. In one study of Genvoya in subjects with a baseline eGFR between 30 and 69 mL/min, 4% of subjects were discontinued due to worsening renal function. No cases of Fanconi syndrome or proximal renal tubulopathy have been reported in clinical trials of Genvoya. Because Genvoya is a fixed dose combination, dosages of individual drug components, such as tenofovir alafenamide or cobicistat, cannot be decreased if renal toxicity occurs. Therefore, Genvoya is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

Individuals with an eGFR less than 90 mL/min/1.73 m^2 were excluded from participation in GS-US-292-0106. Safety monitoring for renal toxicity included analysis of the following laboratory tests: urinalysis with urine chemistry, serum creatinine, eGFR, and phosphorous at screening, baseline and Weeks 1, 4, 4, 8, 12, 16, and 24; fasting urine for retinol binding protein and beta-2

microglobulin at baseline and Weeks 8, 12, and 24; and cystatin C at baseline and at Weeks 4 and 24.

There were no clinical adverse events of the renal organ system.

Serum creatinine and eGFR at baseline and during the trial are shown in the following table.

Table 9: Serum Creatinine and Estimated Glomerular Filtration Rate (eGFRs) during Trial GS-US-292-0106

	Mean (SD*)	Median (Q1, Q3#)
Serum Creatinine (mg/dL)		
Baseline	0.51 (0.072)	0.52 (0.45, 0.55)
Week 4	0.55 (0.093)	0.54 (0.48, 0.61)
Week 24	0.56 (0.088)	0.55 (0.50, 0.62)
Change from baseline to Week 24	+0.05 (0.092)	+0.04 (0.01, 0.29)
eGFR (mL/min/1.73 m^2)		
Baseline	148.7 (20.62)	150.0 (134.7, 165.6)
Week 4	140.4 (23.53)	147.0 (122.0, 160.1)
Week 24	141.1 (22.01)	143.7 (121.8, 161.4)
Change from baseline to Week 24	-7.6 (22.25)	-6.5 (18.7, 5.9)

*SD=standard deviation
#Q1, Q#= first and third quartiles
Source: Clinical Study Report GS-US-292-0106: Text, pages 90-91.

As shown in Table 9, there was a very slight increase in mean and median serum creatinine at Week 4 that persisted through Week 24. Similarly, there was a slight decrease in eGFR at Week 4 that continued through Week 24.

There were no Grade 1 or higher laboratory values for serum creatinine in the trial. There were no Grade 1 or higher laboratory abnormalities for serum phosphorous or for glycosuria. Three subjects (13%) experienced transient Grade 1 proteinuria during the trial. No evidence of renal tubulopathy was observed.

The mean Cystatin C value at baseline was 0.62 mg/dL, and the mean value at Week 24 was 0.69 mg/dL. The difference from baseline to Week 24 was +0.06. The median baseline value of urine retinol binding protein to creatinine ratio was 102.94 µg/g, and the range of results were wide with first and third quartiles of 68.46 and 123.89 respectively. The Week 24 median change in the ratio of retinol binding protein to creatinine was -21.36 (Q1 and Q3 of 14.76 and 184.88). The usefulness of these results is limited due to the wide range of values. Similarly, there was a wide range in urine beta-2-microglobulin to creatinine ratios with a baseline median of 124.1 (93.0, 210.1) and a change of -5.7 at Week 24 (-50.8, 29.3). As a result the urine beta-2-microglbuline levels are also of limited value in evaluating renal toxicity in this small population with considerable variability in baseline values.

Overall, no new or unexpected findings with regard to renal toxicity were found, and the renal-related findings in Trial GS-US-292-0106 were consistent with those observed in adolescent and adult studies of Genvoya.

Bone Mineral Density

Decreases in bone mineral density and pathological bone fractures have been observed in trials of tenofovir prodrugs. Although bone toxicity is less of a concern with tenofovir alafenamide

compared to tenofovir disoproxil fumarate because of lower tenofovir exposure with TAF, bone was one of the two target organs of toxicity in preclinical studies of Genvoya in rats and dogs. Bone safety was monitored by collection of information on all fracture events, measurement of bone mineral density at baseline and Week 24 by dual energy, X-ray absorptiometry (DXA) scan; and measurement of laboratory bone markers.

No bone fractures were reported through Week 24. However, Subject 8122-2071 had a Grade 1 radius fracture on Day 304. The subject is a 9 year old female with cerebral palsy who fell at home and experienced a right radial, Salter-Harris Type II fracture. The subject was placed in a cast that was removed 19 days later. Her total bone mineral density and spine bone mineral density increased from baseline to Week 24 and to Week 48. The fracture was judged by the investigator as related to the fall and not to Genvoya.

DXA scans were assessed by the percentage change from baseline in spine and total body less head (TBLH), and the change from baseline in bone mineral density Z-score for spine and for TBLH. The baseline and change from baseline in bone mineral density are shown in Table 10.

Table 10: Baseline Spine and Total Body Less Head (TBLH) Bone Mineral Density (BMD) and Percent Change from Baseline to Week 24

	Mean Spine BMD (SD)	Mean TBLH BMD (SD)
Baseline (g/cm^2)	0.619 (0.1237)	0.685 (0.0759)
% Change at Week 24	2.937 (4.9459)	1.731 (2.5231)

Source: Clinical Study Report GS-US-292-0106: Table 11-5, page 87.

A decrease in BMD of 4% or greater is considered clinically significant. Two subjects had changes from baseline greater than 4% in spinal BMD: one subject had a -5.276% decline and the other a -6.555% decline; no subjects had a decrease greater than 4% in BMD of the TBLH. These results are similar to results in HIV-infected adults; 1% of adult subjects who switched to Genvoya in GS-US-292-0106 had a 5% or greater decrease in spinal BMD.

The mean baseline bone mineral density Z-scores and the change from baseline in Z-scores are shown in the following table. The BMD Z-scores in the table are adjusted for height-age since height-adjusted Z-scores are typically used to identify whether significant bone loss has occurred.

Table 11: Baseline Spine and Total Body Less Head (TBLH) Bone Mineral Density (BMD) Z-Scores (Height-Age Adjusted) and Percent Change from Baseline to Week 24

	Mean Spine BMD Z-Score(SD)	Mean TBLH BMD Z-Score (SD)
Baseline	-0.56 (0.829)	-0.74 (0.978)
% Change at Week 24	0.05 (0.414)	-0.1. (0.207)

Source: Clinical Study Report GS-US-292-0106: Tables 11-6 and 11.7, pages 87-88.

The mean BMD Z-scores at baseline were decreased and there was little change in Z-scores at Week 24. A BMD Z-score that changes from greater than -2 to -2 or less is considered clinically significant. No subjects had a clinically meaningful change in BMD as measured by Z-score.

The percentage change from baseline to Week 24 was analyzed for all bone laboratory safety parameters. The values of all parameters were similar or higher at Week 24 than at baseline for all laboratory tests except two: bone specific alkaline phosphatase and 1, 25-$(OH)_2$-vitamin D. Median bone specific alkaline phosphatase was 91.65 µg/L at baseline and there was a -10.67% change at Week 24. Baseline 1, 25-$(OH)_2$-vitamin D was 103.1 pg/mL and there was a

-7.8% change at Week 24. In addition, three subjects were diagnosed with vitamin D deficiency during the study. According to the applicant, the changes in bone laboratory values were consistent with the effects of growth, skeletal size, and pubertal maturation.

The findings differ from bone safety findings in adult trials of Genvoya, most likely due to increases in bone size and bone density during the pediatric years. Since there was no comparator arm, it is difficult to interpret the results from GS-US-292-0106. However, there was an increase in bone mineral density at Week 24 and Z-scores were similar at baseline and Week 24. Although one subject experienced a fracture, the fracture occurred after a fall and was not judged as related to Genvoya. In summary, although the data are difficult to interpret, there were no new or unexpected bone safety findings.

Adverse Events with Severe or Life-threatening Intensity
All AEs were Grade 1 or 2 in severity.

Common Adverse Events
A total of 46 adverse drug reactions (ADRs), e.g., adverse events considered Genvoya-related, as assessed by the investigator, were reported in 9 (39.1%) subjects through Week 24 of the study. The most commonly reported ADRs were in the gastrointestinal System Organ Class (6 subjects or 26.1%), and the most commonly reported ADRs and the only ADRs reported in at least 2 subjects were abdominal pain (4 subjects or 17%) and vomiting (4 subjects or 17%).

The ADRs reported were all Grade 1 or 2 in intensity; there were no Grade 3 or 4 AEs or SAEs that were judged as Genvoya–related.

In adult studies of subjects who received Genvoya, the most commonly reported ADRs were nausea, diarrhea, headache, and fatigue (see Genvoya package insert). Although the most commonly reported ADRs in pediatric patients in Trial GS-US-292-0106 differed from those reported in adults, the most commonly reported ADRs in both populations were in the gastrointestinal System Organ Class.

Adverse events of any causality
Most subjects [17/23 (73.9%)] experienced at least one adverse event (AE) through Week 24. The most common AEs (by Preferred Term, all grades, regardless of causality) with incidence reported in at least 10% of subjects are shown in Table 12.

Table 12: Adverse Events (AEs) Reported in ≥10% of Subjects through Week 12 Post-Treatment

Total Number of Subjects	**23**
Number (Percentage) of Subjects with AE	17 (73.9%)
Respiratory tract infection	7 (30%)
Abdominal pain	6 (26%)
Vomiting	5 (22%)
Headache	3 (13%)
Vitamin D deficiency	3 (13%)

Source: Clinical Study Report GS-US-292-0106: Table 11-3, page 85.

The types of commonly reported adverse events were similar to those that were reported as adverse drug reactions in the adolescent cohort of this trial and with those that were reported in Phase 3 trials of adults.

Laboratory Abnormalities
Laboratory abnormalities were reported in 21 (91%) subjects through Week 24. The majority of laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 laboratory abnormalities were reported in 5 (22%) subjects; no Grade 4 laboratory abnormalities were reported. The Grade 3 abnormalities included four subjects with neutropenia; in three subjects the neutropenia was isolated and transient. One of the subjects with Grade 3 neutropenia also had Grade 3 hypocalcemia and Grade 3 hypomagnesemia at Week 4. Another subject had Grade 3 hematuria at Week 16. Aside from neutropenia, the types of Grade 3 and 4 laboratory abnormalities were varied and are consistent with the trial population of treatment-experienced subjects.

Assessments of Growth
There was no clinically significant change in height or weight from baseline to Week 24. The changes from baseline to Week 12 post-treatment in height and weight are shown in Table 13.

Table 13: Mean Change in Growth Parameters from Baseline to Week 24

	Change from Baseline
Height (cm)	+2.3
Weight (kg)	+3.1

Source: Clinical Study Report GS-US-292-0106: Tables 31.1 page 214, 32.1, page 216.

There were increases in absolute height and weight during the 24-week trial. While the Z-score for weight increased, there was no meaningful change in the Z-score for height.

The nine males and 14 females were assessed for Tanner staging at baseline and at Week 24. Of the 9 males, 2 changed from Stage 1 pubic hair to Stage 2 and seven were unchanged. Four males went from Stage 1 genitalia to Stage 2, and five remained unchanged. Of the 14 females, 4 went from Stage 1 pubic hair to Stage 2, while 10 remained unchanged. Three subjects went from Stage 1 to Stage 2 for breast development, 2 subjects went from Stage 2 to Stage 3 breast development, and 9 remained unchanged. Overall, the Tanner staging development was consistent with the age group studied.

Safety Summary
In summary, no new safety signal or changes in the frequency of previously described AEs were identified for Genvoya. Overall, the findings in this pediatric clinical trial are consistent with previously described adverse events observed with the use of Genvoya in HIV-infected subjects.

9. Advisory Committee Meeting
Not applicable.

10. Pediatrics
This application contains pediatric data for subjects from 6 to <12 years of age and weighing at least 25 kg. The pediatric trial design, clinical outcome, and proposed labeling for pediatric patients from 12 to <18 years of age was presented to the PeRC. The PeRC agreed with the Division's proposed plans for labeling.

The submission of the interim Clinical Study Report for GS-US-292-0106 is a complete response to a PREA PMR for the study of Genvoya in patients 6 to <12 years of age and a partial response to a PREA PMR for the study of Descovy in patients 6 to <12 years of age.

Data included in this submission represent a partial response to the Pediatric Written Request for Genvoya. Additional data to satisfy the outstanding elements of the Written Request for Genvoya must be submitted by March 31, 2021.

11. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

12. Genvoya Labeling

The Genvoya labeling has been updated to reflect changes in the indication, extending the population to HIV-1 infected pediatric patients weighing at least 25 kg. The changes with this efficacy supplement primarily affected the following sections. Note, while most of the labeling sections have been agreed upon, the addition of wording related to the decrease in CD4 cell counts is currently being negotiated with the applicant.

1 INDICATIONS AND USAGE

GENVOYA is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of GENVOYA [see Clinical Studies (14)].

2.2 Recommended Dosage

GENVOYA is a four-drug fixed dose combination product containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (TAF). The recommended dosage of GENVOYA is one tablet taken orally once daily with food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

6.1 Clinical Trials Experience

Clinical Trials in Pediatric Subjects:

Safety in Pediatric Patients

The safety of GENVOYA in HIV-1 infected pediatric subjects was evaluated in treatment-naïve subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=23) through Week 24 (cohort 2) in an open-label clinical trial (Study 106) [see Clinical Studies (14.5)]. The safety profile in pediatric subjects who received treatment with GENVOYA was similar to that in adults. One 13-year-old female subject developed unexplained uveitis while receiving GENVOYA that resolved and did not require discontinuation of GENVOYA.

Bone mineral Density Effects:

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Among the subjects in cohort 2 receiving GENVOYA, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two GENVOYA subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

8.4 Pediatric Use

The safety and effectiveness of GENVOYA for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indications and Usage (1) and Dosage and Administration (2.2)]*.

Use of GENVOYA in pediatric patients between the ages of 12 to less than 18 years and weighing at least 35 kg is supported by studies in adults and by a study in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (cohort 1 of Study 106, N=50). The safety and efficacy of GENVOYA in these pediatric subjects was similar to that in adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].*

Use of GENVOYA in pediatric patients weighing at least 25 kg is supported by studies in adults and by an open-label trial in virologically-suppressed pediatric subjects ages 6 to less than 12 years and weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to GENVOYA (cohort 2 of Study 106, N=23). The safety in these subjects through 24 weeks was similar to that in antiretroviral treatment-naïve adults *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].*

11.3 Pharmacokinetics

Pediatric Patients

Mean exposures of elvitegravir, cobicistat, and TAF achieved in 24 pediatric subjects aged 12 to less than 18 years who received GENVOYA in Study 106 were decreased compared to exposures achieved in treatment-naïve adults following administration of GENVOYA, but were overall deemed acceptable based on exposure-response relationships; the emtricitabine exposure in adolescents was similar to that in treatment-naïve adults (Table 9).

Table 9 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	2.2 (19.2)	1.2 (35.0)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	23.8 (25.5)	8.2[b] (36.1)	14.4 (23.9)	0.18 (55.8)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.30 (81.0)	0.03[c] (180.0)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection, cohort 1 of Study 106 (N=24).
b. N=23
c. N=15

Exposures of the components of GENVOYA achieved in 23 pediatric subjects between the ages of 6 to less than 12 years who received GENVOYA in Study 106 were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of

GENVOYA; however, the increase was not considered clinically significant (Table 10) *[see Use in Specific Populations (8.4)]*.

Table 10 Multiple Dose Pharmacokinetic Parameters of Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide (TAF) and its Metabolite Tenofovir Following Oral Administration of GENVOYA in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Elvitegravir	Cobicistat	Emtricitabine	TAF	Tenofovir
C_{max} (microgram per mL)	3.1 (38.7)	2.1 (46.7)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	33.8[b] (57.8)	15.9[c] (51.7)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.37 (118.5)	0.1 (168.7)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection, cohort 2 of 23 Study 106 (N=23).

b. N=22

c. N=20

14 Clinical Studies

14.1 Description of Clinical Trials

Information regarding GS-US-292-0106 was added to the following table.

Table 14 Trials Conducted with GENVOYA in Subjects with HIV-1 Infection

Trial	Population	Study Arms (N)	Timepoint (Week)
Study 104[a] Study 111[a]	Treatment-naïve adults	GENVOYA (866) STRIBILD (867)	144
Study 109[b]	Virologically-suppressed[d] adults	GENVOYA (959) ATRIPLA® or TRUVADA®+atazanavir+cobicistat or ritonavir or STRIBILD (477)	96
Study 112[c]	Virologically-suppressed[d] adults with renal impairment[e]	GENVOYA (242)	96
Study 106 (cohort 1)[c]	Treatment-naïve adolescents between the ages of 12 to less than 18 years (at least 35 kg)	GENVOYA (50)	48
Study 106 (cohort 2)[c]	Virologically-suppressed children between the ages of 6 to less than 12 years (at least 25 kg)	GENVOYA (23)	24

a. Randomized, double blind, active controlled trial.
b. Randomized, open label, active controlled trial.
c. Open label trial.
d. HIV-1 RNA less than 50 copies per mL.
e. eGFR of 30 to 69 mL per minute by Cockcroft-Gault method.

14.4 Clinical Trial Results in HIV-1 Infected Pediatric Subjects Between the Ages of 6 to Less than 18
The following section was added.

Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)

Subjects in cohort 2 treated with GENVOYA once daily had a mean age of 10 years (range: 8-11), a mean baseline weight of 31.6 kg, 39% were male, 13% were Asian, and 78% were Black. At baseline, median CD4+ cell count was 969 cells/mm^3 (range: 603 to 1421), and median CD4% was 39% (range: 30% to 51%).

After switching to GENVOYA, 100% (23/23) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. From a mean (SD) baseline CD4+ cell count of 966 (201.7), the mean change from baseline in CD4+ cell count was -150 cells/mm^3 and the mean (SD) change in CD4% was -1.5% (3.7%) at Week 24. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1) and Pediatric Use (8.4)].*

13. Descovy Labeling
The Descovy labeling has been updated to reflect changes in the indication, extending the population to HIV-1 infected pediatric patients weighing at least 35 kg and pediatric patients weighing at least 25 kg and less than 35kg if the patient is not also receiving a protease inhibitor with a CYP3A inhibitor.

The changes with this efficacy supplement primarily affected the following sections. Note, while most of the labeling sections have been agreed upon, the addition of wording related to the decrease in CD4 cell counts is currently being negotiated with the applicant.

1 Indications and Usage
DESCOVY is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg.

DESCOVY is also indicated, in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor, for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg and less than 35 kg.

2.2 Recommended Dosage
DESCOVY is a two-drug fixed dose combination product containing 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of DESCOVY is one tablet taken orally once daily with or without food in adults and pediatric patients with body weight at least 25 kg and creatinine clearance greater than or equal to 30 mL per minute [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

6.1 Clinical Trials Experience
Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection
In an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg (N=(b) (4) cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at 25 kg (N=23; cohort 2) who received FTC+TAF with EVG+COBI through 24 weeks, the safety of this combination was similar to that of adults.

The following was added under the heading, Bone Mineral Density Effects.
Cohort 2: Virologically-suppressed children (6 to less than 12 years; at least 25 kg)
Among the subjects in cohort 2 receiving FTC+TAF with EVG+COBI, mean BMD increased from baseline to Week 24, +2.9% at the lumbar spine and +1.7% for TBLH. Mean changes from baseline BMD Z-scores were -0.06 for lumbar spine and -0.18 for TBLH at Week 24. Two subjects had significant (at least 4%) lumbar spine BMD loss at Week 24.

8.4 Pediatric Use
The safety and effectiveness of DESCOVY, in combination with other antiretroviral agents, for the treatment of HIV-1 infection was established in pediatric patients with body weight greater than or equal to 25 kg *[see Indication and Usage (1) and Dosage and Administration (2.2)]*.
Use of DESCOVY in pediatric patients between the ages of 12 to less than 18 years weighing at least 35 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 35 kg (N=(b)(4) cohort 1). The safety and efficacy of FTC+TAF with EVG+COBI in these pediatric subjects was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.
Use of DESCOVY in pediatric patients weighing at least 25 kg is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by an open-label trial in virologically-suppressed pediatric subjects between the ages of 6 to less than 12 years weighing at least 25 kg, in which subjects were switched from their antiretroviral regimen to FTC+TAF with EVG+COBI (N=23; cohort 2). The safety in these subjects through 24 weeks of FTC+TAF with EVG+COBI was similar to that of HIV-1 infected adults on this regimen *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.
Safety and effectiveness of DESCOVY coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.2)]*.
Safety and effectiveness of DESCOVY in pediatric patients less than 25 kg have not been established.

12.3 Pharmacokinetics
Pediatric Patients
Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 5).

Table 5 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.18 (55.8)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).
b. N=23

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20 to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 6) *[see Use in Specific Populations (8.4)]*.

Table 6 Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable
a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23)
b. N=22

14 Clinical Studies

(b) (4)

14. Outstanding Issues

None. However labeling negotiations are currently ongoing.

15. Recommendations / Risk Benefit Assessment

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of Genvoya for the treatment of HIV-1 infection in patients weighing at least 25 kg, and the approval of Descovy for the treatment of HIV-1 infection in combination with other antiretroviral drugs of patients weighing at least 35 kg or of patients weighing at least 25 kg but less than 35 kg if the patient is not receiving a protease inhibitor that requires a CYP3A inhibitor.

Throughout the review of this sNDA, no deficiencies that would preclude the approval were identified. Genvoya was studied in a multicenter, open-label, non-comparative trial in which 23 pediatric subjects from 6 to less than 12 years of age were enrolled and followed for 24 weeks. Intensive pharmacokinetic assessment was performed at Week 4 while the safety and efficacy of Genvoya were evaluated through Week 24.

Similar to other pediatric trials which evaluate the safety and effectiveness of ARVs, this trial was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe findings.

The adult dose of Genvoya was administered and intensive PK evaluation was conducted at Week 4. PK parameters were assessed for each of the four components of Genvoya and for the tenofovir alafenamide metabolite tenofovir. PK parameters for elvitegravir, cobicistat, and emtricitabine were compared to historical adult data from Genvoya-treated adults in GS-US-292-0102. PK parameters for TAF and tenofovir were compared to population PK modeling in Genvoya-treated adults in GS-US-292-0104 and GS-US-292-0111. Exposures (AUC, C_{max}, and/or C_{tau}) of TAF, TFV, EVG, COBI, and FTC, except for the EVG C_{tau}, were higher than exposures achieved in adults. The increase in TAF C_{max} is not a concern since the tenofovir exposures were much lower compared to adults administered TDF. Exposure-safety analyses in previous studies of EVG, COBI, and FTC, have not identified exposure-related safety concerns. In addition, no safety concerns were observed in this study. The EVG C_{tau} was slightly lower than the adult comparator with a ratio of pediatric to adult values of 0.855 (lower 90% confidence interval of 0.55); however, the EVG C_{tau} was more than 8-fold above the IC_{95} for wild-type virus. The results support the use of the adult dose of Genvoya, a fixed dose combination administered as one tablet daily, in patients weighing at least 25 kg. The results also support the use of Descovy in patients who weigh at least 35 kg and in patients who weigh at least 25 kg but less than 35 kg and are not receiving a protease inhibitor and CYP3A inhibitor.

The trial was not powered for true statistical analysis of efficacy. However, the results were compared to the efficacy results of the Phase 3 trial of Genvoya in treatment-experienced adults who switched from a stable ARV regimen to Genvoya. The efficacy outcome, as measured by HIV RNA <50 copies/mL, for the overall study population was 100%. The efficacy outcome was similar to that observed in treatment-experienced adults who switched to Genvoya.

A decrease in the mean CD4 cell count was observed at all time points. The mean baseline CD4 count was 966 cells/µL; the mean change at Week 2 was -165 cells which was sustained at Week 24 (-150 cells/µ/L). The reason for the decrease in CD4 cell count after switching from a stable ARV regimen to Genvoya is unclear. However, only a small difference in CD4 cell

count (+33 cells/μL) was observed in the Phase 3 trial of adults who switched to Genvoya. The high CD4 count at baseline may have contributed to this change as evidenced by the mean change in CD4 percentage of only 1.5%. No subjects had CD4 cell counts fall below 400 cells/μL, and no subjects had illnesses consistent with immunosuppression. Information about the mean decrease in CD4 counts will be included in the package insert.

The applicant demonstrated an acceptable safety profile for Genvoya in pediatric patients weighing at least 25 kg. Genvoya was generally safe and well tolerated in pediatric subjects enrolled in this trial. No deaths, serious adverse events, or premature study discontinuations due to adverse events were reported. No new safety concerns were identified. The observed risks of Genvoya use have been described previously, and the rate and nature of adverse events were similar to those in treatment-experienced adults.

The safety and efficacy of Descovy in pediatric patients are supported by prior studies of bioequivalence with bridging of PK data from two of the components of Genvoya to the components of Descovy. Genvoya contains a pharmacokinetic enhancer, cobicistat, while Descovy does not. Because some protease inhibitors affect TAF exposures differently than cobicistat, the use of Descovy with boosted protease inhibitors in children weighing 25 to < 35 kg needs further study. Therefore, the pediatric dose for Descovy is one tablet per day in patients who weigh at least 25 kg but less than 35 kg and are not receiving a boosted protease inhibitor as part of their ARV regimen. Use of Descovy with protease inhibitors is already approved for patients weighing at least 35 kg.

Of note, the size of the safety database in pediatric patients is limited and this trial has continued to follow subjects beyond the Week 24 cutoff. An additional cohort of subjects ages 6 to < 12 is currently enrolling, and data from all subjects will be included in the final clinical study report.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for Other Postmarketing Requirements and Commitments
None. The applicant will continue to submit PADERS and annual reports (DSURs) for review. The current submission partially fulfills the Genvoya Pediatric Written Request, and no additional pediatric post-marketing study commitments will be sought for Genvoya or Descovy. The current submission also fulfills the only PREA PMR (see Section 2.5) for Genvoya and partially fulfills the PREA PMR for Descovy.

16. Clinical Investigator Disclosure Review Template for sNDA 207561/S-14

Submission Date(s): April 3, 2017
Applicant: Gilead Sciences, Incorporated
Product: Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)

Reviewer: Melisse Baylor, MD
Date of Review: September 5, 2017
Covered Clinical Trial (Name and/or Number): GS-US-334-1112

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **58**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0** Significant payments of other sorts: **0** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	**Yes** ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	**Yes** ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason: N/A	**Yes** ☐	No ☐ (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*.

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/s/

PRABHA VISWANATHAN

09/11/2017

This review was submitted by Prabha Viswanathan, the CDTL for these applications, on behalf of Melisse Baylor, the primary clinical reviewer. I concur with Dr. Baylor's recommendation to approve these pediatric efficacy supplements.