Cross-Discipline Team Leader Review

Date	October 7, 2021
From	Samer El-Kamary, MD, MPH Wendy Carter, DO, Cross-Discipline Team Leader Yodit Belew, MD, Acting Deputy Division Director
Subject	Combined Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Memo
NDA# and Supplement#	210251/Supplement 14/Supporting Document number 641/Sequence number 0109
Applicant	Gilead Sciences, Incorporated.
Date of Submission	April 9, 2021
PDUFA Goal Date	October 09, 2021
Proprietary Name	Biktarvy®
Established or Proper Name	bictegravir[BIC]/emtricitabine[FTC]/tenofovir alafenamide[TAF]; B/F/TAF
Dosage Form(s)	Oral tablets: ▪ 50 mg bictegravir, 200 mg emtricitabine, and 25 mg tenofovir alafenamide ▪ 30 mg bictegravir, 120 mg emtricitabine, and 15 mg tenofovir alafenamide
Applicant Proposed Indication(s)/Population(s)	HIV-1 infected (b) (4) weighing ≥ 14 to < 25 kg: For treatment of HIV-1 infection
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Section 12 Labeling)
Recommendation on Regulatory Action	*Approved*

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1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The safety and efficacy data submitted in this efficacy supplement support approval of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®, BIC/FTC/TAF; B/F/TAF) with a lower dose fixed dose formulation of bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg for the treatment of HIV-1 infection in children weighing ≥ 14 to < 25 kg. Throughout the review of this supplemental New Drug Application (sNDA), no deficiencies that would preclude approval were identified. Biktarvy was studied in a multicenter, open-label, non-comparative trial (Study GS-US-380-1474) in which 122 children (100 children 6 to < 18 years and weighing ≥ 25 kg; and 22 children ≥ 2 years of age, and weighing ≥ 14 to < 25 kg), were enrolled and followed for ≥ 24 weeks of study treatment. The trial design comprised two phases: a PK lead-in phase and a treatment phase in which the safety and efficacy of the bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) were evaluated. The B/F/TAF dose was based on the child's weight, with adult tablets tablets for those who weighed ≥ 25 kg (B/F/TAF: 50 mg/200 mg/25 mg), and a low dose tablet (B/F/TAF: 30 mg/120 mg/15 mg) for those weighing ≥ 14 kg to < 25 kg. For subjects unable to swallow the low-dose tablet, the tablet was split and all the parts were swallowed separately within approximately 10 minutes. The study consisted of the three cohorts: Cohort 1 (12 to < 18 years and weighing ≥ 35 kg); Cohort 2 (6 to < 12 years, and weighing ≥ 25 kg) and Cohort 3 (2 to < 6 years, and weighing ≥ 14 kg and < 25 kg). Because B/F/TAF is approved for children 6 to < 18 years and weighing ≥ 25 kg (Cohorts 1 and 2), data for Cohort 3 only are presented in this review, which provides efficacy data through Week 24, and Safety Data through Week 48.

Biktarvy is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults and older children (b) (4) who have no antiretroviral (ART) treatment history or to replace the current ART regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL), on a stable ART regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy. The efficacy of ARVs, including B/T/TAF, in children is based on establishing a dosing regimen in pediatric subjects that results in comparable pharmacokinetic (PK) exposures in children relative to the observed exposures in adults; thus efficacy is extrapolated based on PK bridging. Treatment-naïve pediatric subjects were not included in trial GS-US-380-1474 because the clear majority of pediatric patients in this age range are already on ARV regimen, initiated soon after perinatal diagnosis. Because PK exposure is independent of treatment history, and because the dose is the same for treatment-naïve or virologically suppressed adults, the efficacy of B/F/TAF in treatment-naïve children can be extrapolated from the PK data generated in virologically suppressed children.

The BIC, FTC, and TAF plasma exposures, safety and efficacy in Cohort 3 (≥ 2 years and ≥ 14 to < 25 kg) were similar to those seen in adults and older children (6 to < 18 year old). Because the trial is not powered for statistical analysis of safety or efficacy, the results are presented with descriptive statistics.

The efficacy outcome, as measured by the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 for Cohort 3 was 90.9% (20/22; 95% confidence interval (CI) 70.8% to 98.9%.). Two subjects (9.1%, 2/22) were on the drug but did not have virologic data collected at the Week 24 visit because of COVID-19 pandemic-related travel disruption. There was no evidence of virologic failure and among the 20 subjects with available HIV-1 RNA viral load, 20/20 (100%) achieved the efficacy outcome. B/F/TAF was found to be safe and well tolerated and the most commonly observed drug-related adverse events (AE) were similar to those seen in adults and were mild in nature (neutropenia, abdominal pain, constipation, irritability, nausea and social avoidant

behavior). There were no Grade 3 or higher AEs, no serious adverse events (SAE) and no deaths reported. There were no discontinuations due to an AE. All the laboratory AEs were Grade 1 or 2, except for one Grade 3 elevated alkaline phosphatase at Week 48 that resolved by Week 60. There were no relevant changes from baseline in vital sign parameters and no changes from baseline in height and height Z-scores. The body weight and body weight Z-scores increased (as expected) during the study.

During the review, we identified the (b) (4) –as a potential review issue. The ability of children < 3 years of age to consistently swallow a daily tablet (14 x 6.5mm) for a chronic condition was of particular concern; and no children younger than 3 years of age were enrolled in this study to provide use-data from the trial. The Applicant acknowledged that some children (the youngest were 3 years of age) indeed had difficulty swallowing the whole tablet in this study, but they were able to swallow it uneventfully after splitting the tablet and ingesting the parts (~7 mm x 6.5 mm each) within 10 minutes. Note, since the formulation of the proposed tablets is an immediate release (b) (4) tablet (b) (4), splitting, crushing or chewing the tablet would not reduce the bioavailability of the drug, provided all the parts are consumed within approximately 10 minutes. In addition, the applicant also provided other published articles describing how children as young as two years of age were able to swallow tablets 5-9 mm without difficulty. Ultimately, after considering the available information, and based on the benefit-risk assessment, the team determined that the labeling should be inclusive of pediatric patients (b) (4) weighing at least 14 kg. Language is also included on splitting the low-dose tablet and ingesting the parts within approximately 10 minutes. Lastly, the labeling clarifies that no children younger than 3 years were enrolled in the clinical trial.

In conclusion, after review of the data from the study, we have determined that the benefit of B/F/TAF for the treatment of HIV infection outweighs the risks, and recommend approval of B/F/TAF (bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg (Biktarvy®) for the treatment of HIV-1 infection in children who are both treatment naïve and virologically suppressed and weighing ≥ 14 kg to < 25 kg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection is a life-threatening and serious disease of major public health significance. • Approximately 38 million people infected worldwide, including an estimated 1.7 million children (range 1.3 to 2.2 million) under 15 years of age. • Globally, approximately 160,000 children under 14 years of age acquired HIV in 2018. • There is no vaccine and no post-exposure immunoprophylaxis available for HIV.	HIV-1 remains a major cause of morbidity and mortality worldwide. If untreated, HIV-1 is a life-threatening condition, one that affects a large population. HIV-1 infection is a significant public health concern.
Current Treatment Options	• Integrase Strand Transfer Inhibitors (INSTIs) in combination with two Nucleoside reverse transcriptase inhibitors (NRTIs) have become a preferred regimen for HIV treatment as recommended by the Department of Health and Human Services HIV treatment guidelines for children, adolescents and adults. • Seven single tablet regimens (STRs) are currently approved for once daily administration in the treatment of HIV-1 infection in adolescents and/or children including: o Bictegravir/emtricitabine/tenofovir alafenamide [TAF] (Biktarvy®) o Rilpivirine/emtricitabine/TAF (Odefsey®) o Efavirenz/ emtricitabine /tenofovir disoproxil fumarate [TDF] (Atripla®) o Emtricitabine /rilpivirine/TDF (Complera®/Eviplera®) o Elvitegravir/cobicistat/emtricitabine/TDF (Stribild®) o Elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®; GEN) o Abacavir/dolutegravir/lamivudine (Triumeq®) • Fixed-dose combination (FDC) STR treatments are a convenient option for treatment; however, in those weighing less than 25 kg there are fewer fixed dose combination (FDC) or STR options.	• A once daily single-tablet regimen has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for people living with HIV-1. • Many pediatric patients would also benefit from the availability of a simplified, once daily, STR that combines potent efficacy, tolerability, a favorable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing • Moreover, a TAF-containing regimen would be a better choice than a TDF-based regimen in this population due to a more favorable bone and renal toxicity profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• To support an efficacy claim for the use of B/F/TAF for the treatment of HIV infection in children [redacted] (b) (4) ≥ 14 kg and < 25 kg, the applicant submitted the 24-week efficacy and safety results from a single study (Study Trial GS-US-380-1474), which is a Phase 2/3, open-label, multicenter, multicohort, non-comparator trial. • In this study, 22 children weighing ≥ 14 to 25 kg (age range 3 to 9 years old) with virologically suppressed HIV infection, were treated with B/F/TAF once daily for 24 weeks. • The study demonstrated a high efficacy among those who received treatment: o Twenty subjects (20/22; 90%) achieved the efficacy outcome of plasma HIV-1 RNA <50 copies/mL at Week 24. o There was no evidence of virologic failure, and among the 20 subjects with available HIV-1 RNA viral load, all (100%) achieved the efficacy outcome. • Exposures of B/F/TAF components and tenofovir, a prodrug of TAF, in trial subjects were considered acceptable and supported the conclusion that the exposures observed in this weight (age) group are comparable to the exposure observed in adults who received the recommended dose.	• B/F/TAF provided durable virologic suppression in this pediatric population. • It is well known that long-term viral suppression in children would also prevent or lead to fewer complications later in their life.
Risk and Risk Management	• Subjects administered Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide; BIC/FTC/TAF; B/F/TAF) reported few mild side-effects (neutropenia, abdominal pain, constipation, irritability, nausea and social avoidant behavior), all of which were considered mild (Grade 1 or 2 AEs). There were no deaths or drug-related SAEs. • There were no premature discontinuations of treatment due to an AE. All the laboratory AEs were Grade 1 or 2, except for one Grade 3 laboratory abnormality of an elevated alkaline phosphatase at Week 48 that resolved by Week 60. • The CD4 cell count by Week 24 dropped slightly but was not significantly different than the baseline level. The mean change from baseline to Week 24 in CD4+ cell count (SD) was −126 (264.2) cells per mm^3; and the mean change in CD4% (SD) from baseline to Week 24 was 0.2% (4.4%). • There were no notable effects of treatment on development or growth (baseline to Week 24) in Tanner stage, bone age, height, weight and Body Mass Index (BMI)	The frequency of adverse events observed in this study were generally mild and similar to those noted in adolescents and adults. There were , with negligible changes in CD4 count and percentage. Based on the available safety profile for B/F/TAF, no Risk Evaluation and Mitigation Strategy (REMS) is recommended at this time.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	percentiles, and vital signs.	

Patient Experience Data

Patient Experience Data for Biktarvy® in children [redacted] (b) (4) weighing ≥ 14 to < 25 kg with HIV infection were collected within the clinical trials. The table below presents where Patient Experience Data Relevant to this Application is described in Study GS-US-380-1474. See Appendix 1 for a summary of the data collected in this study.

Patient Experience Data Relevant to this Application (check all that apply)

♦	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	♦	Clinical outcome assessment (COA) data, such as		-
		♦	Patient reported outcome (PRO)	Study GS-US-380-1474 Interim Analysis 2 Clinical Study Report (CSR) Synopsis; Clinical Study Report, Section 12.1, Tables 15.11.7.3.1.2 and 15.11.7.3.2.2; M2.5 Clinical Overview Section 2.3
		♦	Observer reported outcome (ObsRO)	Study GS-US-380-1474 Interim Analysis 2 CSR Synopsis; Clinical Study Report, Section 12.1, Tables 15.11.7.3.1.2 and 15.11.7.3.2.2; M2.5 Clinical Overview Section 2.3
		□	Clinician reported outcome (ClinRO)	-
		□	Performance outcome (PerfO)	-

	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		-
	□	Patient-focused drug development or other stakeholder meeting summary reports		-
	□	Observational survey studies designed to capture patient experience data		-
	□	Natural history studies		-
	□	Patient preference studies (e.g., submitted studies or scientific publications)		-
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	-
		□	Patient-focused drug development or other stakeholder meeting summary reports	-
		□	Observational survey studies designed to capture patient experience data	-
		□	Other: (Please specify)	-
□	Patient experience data was not submitted as part of this application. -			

2. Background

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38 million people infected worldwide, including an estimated 1.7 million children (range 1.3 to 2.2 million) under 15 years of age {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2018}. Globally, approximately 160,000 children under 14 years of age acquired HIV in 2018. Of the estimated 4400 HIV infections that occur each day globally in adults and adolescents aged 15 years and older, about 32% are in young people 15 to 24 years of age {UNAIDS 2019}. Standard of care for the treatment of HIV-1 infection uses combination antiretroviral (ARV) therapy (ART) to suppress viral replication to below detectable limits, allow CD4 cell counts to increase, and stop disease progression. For ART-naive HIV-1 infected patients, current treatment guidelines recommend that initial therapy consist of 2 nucleo(s/t)ide reverse transcriptase inhibitors (N[t]RTIs) in combination with a third agent (a nonnucleoside reverse transcriptase inhibitor [NNRTI], a boosted protease inhibitor [PI], or an integrase strand-transfer inhibitor [INSTI]) for the treatment of pediatric patients with HIV infection, depending on age and sexual maturity rating {Department of Health and Human Services (DHHS) 2018}. Virologically suppressed HIV-infected patients may switch from their current regimen because of safety or tolerability concerns or for regimen simplification.

A once daily single-tablet regimen (STR) has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for patients infected with HIV-1 {Airoldi 2010, Bangsberg 2010, Dejesus E 2009, Hodder 2010, Sax 2015}. Many pediatric patients would also benefit from the availability of a simplified, once daily, STR that combines potent efficacy, tolerability, a favorable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing. Eight STRs are currently approved for once daily administration in the treatment of HIV-1 infection in adolescents and/or children: bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (Biktarvy®, BVY; approved in the United States); rilpivirine/FTC/TAF (Odefsey®); efavirenz (EFV)/FTC/tenofovir disoproxil fumarate (TDF) (Atripla®); FTC/rilpivirine/TDF (Complera®/Eviplera®); elvitegravir (EVG)/cobicistat (Tybost®; COBI)/FTC/TDF (Stribild®; STB); EVG/COBI/FTC/TAF (Genvoya®; GEN); and abacavir/dolutegravir/lamivudine (Triumeq®).

The Applicant, (Gilead Sciences [Gilead]) has coformulated INSTI BIC with FTC (F) and TAF into a fixed-dose combination (FDC) tablet suitable for once-daily use without a boosting agent. The B/F/TAF FDC provides a potent, convenient, well tolerated and practical regimen for the long-term treatment of HIV and was approved for use in adult patients in the US on February 7, 2018, and in the European Union on June 21, 2018. The B/F/TAF FDC has now been added to the Department of Health and Human Services guidelines for the treatment of HIV-1 in adults {Panel on Antiretroviral Guidelines for Adults and Adolescents 2018} and is one of the initial regimens recommended by the International Antiviral Society – USA Panel {Saag 2018}.

B/F/TAF provides an alternative therapy for pediatric patients who may not tolerate other agents such as ritonavir (RTV)-boosted PIs or central nervous system adverse events (AEs) due to EFV. Moreover, a TAF-containing regimen is a better choice than a TDF-based regimen in this population due to a more favorable bone and renal toxicity profile. The Phase 2/3 open-label study described in this application is currently ongoing and was conducted to characterize the pharmacokinetics (PK) and confirm the dose of B/F/TAF in adolescents and children, and to

evaluate the safety, tolerability, and antiviral activity of B/F/TAF in HIV-1 infected pediatric subjects.

The Clinical Study Report submitted in this supplemental NDA (210251, Supplement # 14) describes an interim analysis of the study performed when all subjects in Cohort 1 (adolescents 12 to < 18 years of age and weight ≥ 35 kg) and Cohort 2 (children 6 to < 12 years of age and weight ≥ 25 kg) had completed their Week 96 visit, and all subjects in Cohort 3 (children ≥ 2 years of age and weight ≥ 14 to < 25 kg) had completed their Week 24 visit.

The B/F/TAF FDC was approved for use in adolescents and children (6 to < 18 years of age, weighing ≥ 25 kg) in the US on June 18, 2019. **The report provided here describes the review of the data provided for Cohort 3 only**.

2.1. Product Information

Biktarvy® tablets contain bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF; B/F/TAF) for oral administration. Bictegravir is an integrase inhibitor class; emtricitabine is a nucleoside reverse-transcriptase inhibitor (NRTI); and tenofovir alafenamide is a prodrug of tenofovir, a nucleotide analogue reverse transcriptase inhibitor.

Tablets

There are two fixed-dose combination tablet strengths available:

- *Adult strength tablet: 50 mg of Bictegravir; 200 mg of emtricitabine; and 25 mg of tenofovir alafenamide*
- *Low-dose tablet: 30 mg of Bictegravir; 120 mg of emtricitabine; and 15 mg of tenofovir alafenamide*

2.2. Summary of Regulatory Activity Related to Submission

Study GS-US-380-1474 is a required pediatric assessment under section 505B(a) of the Food, Drug and Cosmetic Act (FDCA).

- This required pediatric assessment was issued in the initial approval letter for Biktarvy NDA 210251 dated February 7, 2018.
- An sNDA with safety and efficacy data in HIV-1 infected, virologically suppressed adolescents and children in Study GS-US-380-1474 (Cohort 1: 12 to < 18 years of age, weighing ≥ 35 kg; and Cohort 2: 6 to < 12 years of age, weighing ≥ 25 kg) was submitted on December 20, 2018 (NDA 210251/SN050).
- The supplement was approved on June 18, 2019 and partially fulfilled postmarketing requirement (PMR) 3322-1 (6 to < 18 years, weighing ≥ 25 kg).
- The submission of Week 24 data from Study GS-US-380-1474 Cohort 3 (≥ 2 years of age weighing 14 to < 25 kg) will fulfill the remainder of the PMR 3322-1, which states the following:

> *Conduct a study in patients 2 years to <18 years old who are HIV-1 infected, 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 bictegravir/emtricitabine/tenofovir alafenamide as part of a fixed dose combination (FDC) product. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.*

Study GS-US-380-1474 data in subjects ages 2 years to < 18 years also addresses the clinical study #2 outlined in the Written Request (WR) (b) (4) dated July 22, 2020. Gilead agreed to the terms of the Pediatric WR (b) (4) in NDA 210251/SN0081 submitted on July 22, 2020.

As per this review, 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 (see Section 11.2. Compliance with Good Clinical Practices).

2.3. Summary of Study Protocol

Trial GS-US-380-1474, entitled, *A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Adolescents and Children (Amendment 5, 23 June 2020)*; is an ongoing, open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of the B/F/TAF FDC in HIV-1 infected pediatric subjects.

Protocol version/Date (see section 2.4 Protocol Amendments)
Original: March 17, 2016
Amendment 1: November 9, 2016
Amendment 2: July 24, 2018
Amendment 3: August 27, 2018
Amendment 4: June 13, 2019
Amendment 5: June 23, 2020

Study Design

Approximately 120 subjects were planned to be enrolled: a total of 50 adolescents (Cohort 1: 12 to < 18 years of age), 50 children (Cohort 2: 6 to < 12 years of age), and 20 children (Cohort 3: ≥ 2 years of age).

Within each of 3 cohorts, this study consisted of two parts: Part A which is an intensive PK phase, and a Part B, which is a treatment phase:

- Cohort 1: Adolescent subjects 12 to < 18 years old and and weighing ≥ 35 kg
- Cohort 2: Pediatric subjects 6 to < 12 years old and weighing ≥ 25 kg
- **Cohort 3: Pediatric subjects 3 to < 6 years old and weighing ≥ 14 to < 25 kg**

Pharmacokinetic Phase (Part A)

The intensive PK phase evaluated and confirmed the age-appropriate B/F/TAF dose by analyzing the PK, safety, and antiviral activity of B/F/TAF through Week 2 or Week 4, after which they continued to receive B/F/TAF through Week 48.

Treatment Phase (Part B)

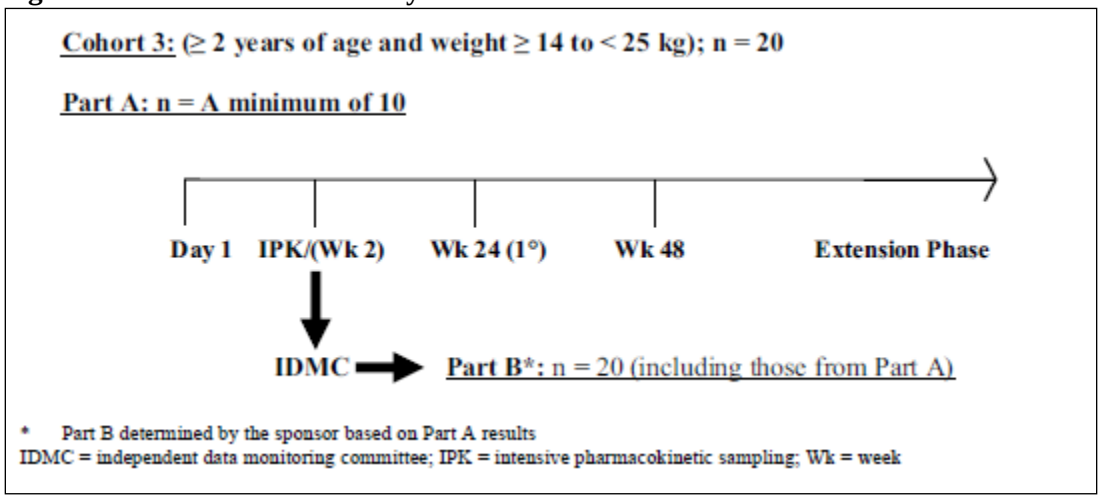
Subjects who completed the intensive PK phase (Part A) were immediately enrolled into the treatment phase (Part B) with no interruption of study drug administration until the appropriateness of the dose had been confirmed by PK and safety results from the PK phase. Additional subjects were enrolled into the treatment phase upon confirmation of the appropriateness of the dose from the PK phase.

For **Cohort 3 (≥ 2 years of age and weight ≥ 14 to < 25 kg),** at least 10 subjects participated in an intensive PK evaluation at Week 2. Once confirmation of the BIC PK and short-term safety data from Cohort 3, Part A were reviewed and considered acceptable by the Independent Data Monitoring Commmittee (IDMC), at least 20 subjects (including those from Part A) were enrolled to receive the low-dose B/F/TAF 30/120/15 mg FDC tablet through Week 48.

At the Week 48 visit, subjects are given the option of receiving B/F/TAF in an open-label extension phase until it becomes available for use according to a subject's age and weight, or through an access program.

A study schema is provided in **Figure 1**.

Figure 1. GS-US-380-1474: Study Schema for Cohort 3



Duration of Treatment

Subjects will be treated for at least 48 weeks. All subjects participating in the extension phase of the study after Week 48 will return for study visits every 12 weeks.

Objectives (for Cohort 3 only)

For details on Cohorts 1, 2 and 4, see pp 211-368 Protocol Version Amendment 5 (23 June 2020)

The primary objectives of Cohort 3 are:

1. **Part A:**
   - To evaluate the steady state PK of BIC and confirm the dose of B/F/TAF 30/120/15 mg FDC in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.
2. **Parts A and B:**

- To evaluate the safety and tolerability of the low dose B/F/TAF FDC tablet through Week 24 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.

The secondary objectives of this study are:

- To evaluate the safety and tolerability of the low dose B/F/TAF FDC tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.
- To evaluate the antiviral activity of the low dose B/F/TAF FDC tablet through Weeks 24 and 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg.

The primary endpoints of this study (Cohort 3) are:

- The steady state PK parameters AUC_{tau} and C_{tau} (C_{trough}) for BIC at Week 2 only.
- Incidence of treatment-emergent AEs, and treatment-emergent laboratory abnormalities through Week 24.

The secondary endpoints of this study are:

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm.
- Change from baseline in CD4+ cell counts and percentages at Weeks 24 and 48.
- PK parameters of AUC_{last}, C_{max}, T_{max}, $T_{1/2}$, apparent CL and apparent V_z for BIC, as applicable; AUC_{tau}, AUC_{last}, C_{max}, C_{tau}, T_{max}, $T_{1/2}$, apparent CL and apparent V_z for TAF and FTC, as applicable.
- Incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through week 48.
- Acceptability and palatability of B/F/TAF formulation.

Inclusion Criteria (Cohort 3)

Subjects must meet **all** of the following inclusion criteria to be eligible for participation in this study.

1. Age ≥ 2 years
2. Body weight at screening: ≥ 14 to < 25 kg (≥ 31 to < 55 lbs)
3. Subject is able to provide written assent if they have the ability to read and write (if applicable per their local institutional guidelines and local country regulations).
4. Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements.
5. Confirmed HIV infection
6. Adequate renal function: Estimated Glomerular Filtration Rate (eGFR) ≥ 90 mL/min/1.73 m^2 (≥ 1.5 mL/sec/1.73 m^2) for children ≥ 1 year of age using the Schwartz Formula.
7. Adequate hematologic function defined as:
   a. Absolute neutrophil count > 500 cells/mm^3 (> 0.50 GI/L)
   b. Hemoglobin > 8.5 g/dL (≥ 85 g/L)

c. Platelets ≥ 50,000/mm^3 (≥ 50 GI/L)
8. Hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN).
9. Total bilirubin ≤ 1.5 mg/dL (≤ 26 μmol/L), or normal direct bilirubin.
10. Documented plasma HIV-1 RNA < 50 copies/mL on a stable regimen for ≥ 6 months preceding the Screening visit.
11. Stable antiretroviral regimen of 2 NRTIs in combination with a third agent for a minimum of 6 months prior to the screening visit.
12. Plasma HIV-1 RNA < 50 copies/mL at the screening visit
13. Life expectancy ≥ 1 year.
14. Have no documented or suspected resistance to FTC, TFV, or INSTIs including, but not limited to, the reverse transcriptase resistance mutations K65R.

Exclusion Criteria (Cohort 3)

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1. CD4+ cell count < 200 cells/ mm^3.
2. An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening.
3. An ongoing serious infection requiring systemic antibiotic therapy at the time of screening
4. Evidence of active pulmonary or extra-pulmonary tuberculosis within 3 months
5. Acute hepatitis in the 30 days prior to study entry
6. Hepatitis B virus (HBV) surface antigen (HBsAg) positive
7. Hepatitis C virus (HCV) antibody positive with detectable HCV RNA.
8. Have any serious or active medical or psychiatric illness which, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include **uncontrolled** renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment within 30 days prior to Day 1.
9. Subjects experiencing decompensated cirrhosis (eg, ascites, encephalopathy)
10. A history of, or ongoing, malignancy.

Study Procedures (Cohort 3)

At the Screening, Day 1, and all subsequent study visits laboratory analyses (hematology, chemistry and urinalysis), HIV-1 RNA, CD4+ cell count, vital signs, complete or symptom-directed physical examinations and estimated GFR using the Schwartz Formula will be performed.

Subjects enrolled in Part A will participate in an Intensive PK evaluation at Week 2. Samples will be collected at 0 (pre-dose, ≤ 30 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours post-dose. Subject diary cards will be provided to all Part A subjects (or parent/legal guardian as needed) to record administration of study drugs prior to the Intensive PK visit.

Fasting glucose and lipid panel (total cholesterol, high-density lipoproteins [HDL], direct low-density lipoproteins [LDL], and triglycerides) will be collected at Day 1, Week 24, and Week 48.

Resistance testing will be performed in subjects who experience virologic rebound, if HIV-1 RNA is ≥ 200 copies/mL.

Palatability and acceptability assessment will be performed at Day 1 and Week 4, at Week 24 and Week 48.

Subjects who prematurely discontinue from the study before Week 48 and subjects who do not wish to continue in the study after completing Week 48 will be required to return to the clinic 30 days after the completion of study drug for a 30-Day Follow-Up Visit.

After Week 48, all subjects will be given the option to participate in an open-label extension phase of the study.

Adverse events and concomitant medications will be assessed at each visit.

Statistical Analyses (Cohort 3 only)
Please see Section 7.1 Statistical Analysis.

2.4. Protocol Amendments

The original protocol (17 March 2016) was amended 5 times (on 09 November 2016, 24 July 2018, 27 August 2018, 13 June 2019, and 23 June 2020) prior to this interim analysis. Key changes to the study protocol are described below for each amendment.

Protocol Amendment 1 (09 November 2016)

- Clarification that the number of subjects to be enrolled in each cohort in Part A was a minimum (rather than total) number
- Correction made to the prior and concomitant medications table
- A body weight cutoff and B/F/TAF dose were specified for Cohort 2 subjects
- The visit window for the Week 24 visit was modified from ± 4 days to ± 4 weeks from the protocol-specified date to align with the statistical window
- The timing of intensive PK and trough PK sampling was amended to allow intensive PK sampling at Weeks 2 or 4 and trough PK sampling at Weeks 1, 2, or 4
- Requirements for attendance at early study drug discontinuation (ESDD) and 30-Day Follow-up Visits were extended to include subjects who prematurely discontinue study drug during the open-label extension phase.

Protocol Amendment 2 (24 July 2018)

- Updated administrative details and Section 1 (Introduction)
- Added Cohort 3 (children ≥ 2 years of age, with weight at screening ≥ 14 to < 25 kg)
- Clarified dosing of Cohorts 1 and 2 with the adult-strength B/F/TAF 50/200/25 mg tablet, and dosing for Cohort 3 with the low-dose B/F/TAF 30/120/15 mg tablet

Protocol Amendment 3 (27 August 2018)

- Added acceptability and palatability assessments at Weeks 24 and 48 for Cohort 3.

Protocol Amendment 4 (13 June 2019)

- Correction made to the exclusion criterion for prior medications to clarify that subjects on a prior ARV treatment regimen must continue until their scheduled Day 1 visit to ensure a seamless transition to the study regimen.
- The eligibility worksheet was removed.

Protocol Amendment 5 (23 June 2020)

- Added Cohort 4 Groups 1-4 to evaluate the safety and tolerability of B/F/TAF for oral suspension in HIV-1 infected, virologically suppressed children (≥ 2 years of age, with weight ≥ 14 to < 25 kg) who are unable to swallow tablets.
- Removed "virologically suppressed" from the protocol title with the addition of the Cohort 4 subject population that includes treatment-naive subjects.

Changes from Planned Analyses

The following were changes from planned analyses:

- For Cohorts 1 and 2, post hoc, AUC_{tau}, C_{max}, and C_{tau} for FTC and TFV, and AUC_{tau}, AUC_{last}, and C_{max} for TAF were compared with intensive PK data from HIV-1 infected pediatric subjects (adolescents 12 to < 18 years of age and children 6 to < 12 years of age) who received GEN (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) in Study GS-US-292-0106.
- Statistical comparisons for AUC_{tau}, C_{max}, and C_{tau} for BIC, FTC, and TFV, and AUC_{tau}, AUC_{last}, and C_{max} for TAF were performed with intensive PK data from preceding cohorts: Cohort 2 compared with Cohort 1, and Cohort 3 compared with Cohorts 1 and 2.
- Due to disruption in study conduct as a result of the COVID-19 pandemic, some efficacy and/or safety assessments were not conducted.
- For Cohort 3, sensitivity analyses were performed in respect of the main efficacy endpoint (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) and palatability/acceptability assessments, in which subjects who switched from the low-dose B/F/TAF 30/120/15 mg tablet to the adult-strength B/F/TAF 50/200/25 mg tablet by virtue of having attained a weight ≥ 25 kg during the main phase of the study were excluded from the Full Analysis Set (FAS) and Safety Analysis Sets, respectively, at the appropriate time points.

3. Product Quality

Adult-Strength Tablet

No new information was submitted in relation to the adult-strength tablet (B/F/TAF 50/200/25 mg). The B/F/TAF 50/200/25 mg FDC is currently indicated in the US as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥ 25 kg who have no antiretroviral (ARV) treatment history, or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of BVY.

Low-Dose Tablet

The designated commercial drug product is an immediate-release FDC tablet containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF. The low-dose B/F/TAF 30/120/15 mg tablet, was developed to support the Phase 2/3 Study GS-US-380-1474 in pediatric patients with HIV-infection and is the proposed commercial tablet formulation. The low-dose B/F/TAF 30/120/15 mg tablet is a (b) (4) tablet.

The adult dose tablets are already approved for use in pediatric patients and adults weighing > 25 kg. The low dose-tablet forumalation was developed for use in children ≥ 2 years of age and weighing ≥ 14 kg to < 25 kg.

The review by the Chemistry, Manufacturing and Control (CMC) team determined that the information submitted by the Applicant in this supplement is acceptable and that it is recommended for approval with no Comments/Deficiencies to be Conveyed to Applicant Please refer to the full review by the CMC reviewer, Dr. Rishi Thakur, for details.

4. Nonclinical Pharmacology/Toxicology

The Pharm-Tox review for this supplement only included toxicological assessments of some newly identified formulation components, that were found to be acceptable. In this respect, Dr. John Dubinion, the Pharm-Tox reviewer, communicated his assessment to the CMC reviewer, Dr. Rishi Thakur, and all the nonclinical information for this NDA supplement were included in the CMC review. *Please refer to the full CMC review by Dr. Rishi Thakur.*

5. Clinical Pharmacology

Pharmacokinetic (PK), safety and efficacy data of Cohort 3 from trial GS-US-380-1474 constitute the totality of evidence supporting the Applicant's proposed dosing regimen for HIV-1 infected pediatric patients (b) (4) weighing 14 kg to < 25 kg. The PK data are considered pivotal in supporting the efficacy of B/F/TAF in this population.

A minimum of 10 evaluable subjects from Part A would provide at least 90% power for BIC AUCtau and Ctau to conclude exposure equivalence between children and adult subjects. A minimum of 10 evaluable subjects from Part A would also provide > 99% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance and volume of distribution of BIC.

In summary, the observed exposure for bictegravir and TAF were generally comparable to the exposures observed in adults at the recommended B/F/TAF dose; any observed or estimated differences in exposure between Cohort 3 and adults and/or Cohorts 1 and 2 were not clinically significant. The B/F/TAF exposure data submitted in this study report support the use of B/F/TAF 30/120/15 mg for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg to less than 25 kg.

Please refer to the full review by Dr. Xing Jing, Clinical Pharmacology, for details.

6. Clinical Microbiology

The antiviral and resistance data through Week 24 (Cohorts 3A and 2B) and Week 48 (Cohort 3A) from Study GS-US-380-1474 support the use of low dose Biktarvy for the treatment of HIV-1 infection in children weighing ≥14 to <25 kg. In virologically-suppressed HIV-1-infected pediatric subjects (weighing ≥ 14 to <25 kg), high rates of virological suppression (HIV-1 RNA levels <50 copies/mL) were maintained through Week 24 in Cohorts 3A and B subjects (90.9%, n = 20/22, missing n = 2) and through Week 48 in Cohort 3A subjects (91.7%, n = 11/12, missing n = 1) treated with adult dose or low dose Biktarvy in Study GS-

US-380-1474. No subject in Cohort 3A qualified for resistance testing through Week 48 or in Cohort 3B through Week 24. The pre-baseline HIV-1 sample of one Cohort 3A subject carried the HIV-1 RT RAS M184V, which confers reduced susceptibility to the BVY component FTC, as well as cross-resistance to lamivudine. Nonetheless, the subject maintained HIV-1 viral suppression through Week 48.

Please refer to the full review by Dr. Anamaris ColbergPoley, Clinical Microbiology, for details.

7. Clinical Efficacy

7.1. Statistical Analysis Plan

As trial GS-US-380-1474 is a single arm trial, no formal statistical testing were conducted. Descriptive statistics are provided to describe the efficacy outcome.

Subject Enrollment and Disposition
The number and percentage of subjects enrolled in each country and at each site was summarized using the Safety Analysis Set. A summary of subject disposition was provided for all screened subjects. This summary included the number of subjects screened, screen failure subjects who were not enrolled, subjects who met all eligibility criteria and were not enrolled, subjects enrolled, subjects enrolled but never treated, subjects in the Safety Analysis Set, and subjects in the full analysis set (FAS).

Demographic and Baseline Characteristics
Subject demographic data (eg, age, sex at birth, race, and ethnicity) and baseline characteristics (eg, body weight, weight Z-score, height, height Z-score, body surface area [BSA], body mass index [BMI], and Tanner stage [genitalia or breasts]) were summarized using descriptive statistics by cohort and total for all subjects in the Safety Analysis Set..

Study drug adherence was computed as the number of pills taken divided by the number of pills prescribed. Descriptive statistics for overall adherence to study drug up to the Week 24 visit, the Week 48 visit, and the data-cut date, along with the number and percentage of subjects in specific adherence categories (eg, < 80%, ≥ 80% to < 90%, ≥ 90% to < 95%, ≥ 95%) were provided for the Safety Analysis Set. No inferential statistics were provided.

Interim Analysis and Data Monitoring
An external Independent Data Monitoring Commmittee (IDMC) was established to review the progress of, and efficacy and safety data from, this ongoing study. A Cohort 3 Part A IDMC analysis was conducted after all subjects enrolled in Part A had completed the intensive PK evaluation at Week 2 and more than half had completed the Week 12 visit or prematurely discontinued from the study. The purpose of this analysis was to determine whether dosing could be initiated for Cohort 3 Part B.

- Interim Analysis 1

This analysis was conducted after all subjects in Cohort 1 Parts A and B and all subjects in Cohort 2 Part A had completed Week 48 of the study, and all subjects in Cohort 2 Part B had completed Week 24 of the study.

- Interim Analysis 2

This analysis was conducted after all subjects in Cohorts 1 and 2 Parts A and B had completed Week 96 of the study, and all subjects in Cohort 3 Parts A and B had completed Week 24 of the study.

7.2. Disposition of Subjects

Subjects in Cohort 3 (n=22) were enrolled and treated at a total of 14 study centers in 4 countries (South Africa [n=11], Thailand [n=5], Uganda [n=2], United States [n=4]). Of the 22 subjects screened, all were enrolled and received study drug up to Week 24. *Six subjects switched from the low-dose B/F/TAF 30/120/15 mg tablet to the adult-strength B/F/TAF 50/200/25 mg tablet upon attaining a weight ≥ 25 kg, 1 at Week 4, 2 at Week 12, 2 at Week 36, and 1 at Week 60.*

At the data-cut date (June 25, 2020), 54.5% (12 of 22) of treated subjects had completed study drug in the main (48-week treatment) phase, and 45.5% (10 of 22) of subjects were continuing to receive study drug in the main phase. No subject prematurely discontinued study drug in the main phase. At the data-cut date, all 12 subjects who completed the study drug in the main phase had entered the extension phase and were continuing to receive study drug.

On July 1, 2021, the Applicant submitted a 90 Day Safety Update (NDA 210251, SN0118) which provided cumulative safety data for all subjects who had received at least 1 dose of study drug by the most recent data-cut date of April 9, 2021.

> *Through the safety update data-cut date (April 9, 2021), all 22 subjects had completed their Week 48 visit in the main phase and entered the extension phase. Nineteen subjects were continuing to receive study drug in the extension phase, and 3 subjects had completed both study drug and the study (including the extension phase). No subject prematurely discontinued the study drug in the extension phase.*

7.3. Protocol deviations

There were a total of 10 important protocol deviations that occurred in 8 subjects, and 11 non-important protocol deviations reported. The 10 important protocol deviaitions are listed below and are mostly related to obtaining an informed consent form (ICF), missing data in the form of incomplete lab work or, or missed appointments or labs not collected due to COVID-19 related travel restrictions.

1. Subject (b) (6)
    a. Missing data - Intensive PK not performed in its entiretly
    b. Missing data - HIV-1 RNA samples not collected for Weeks 24 and 48 visits.
2. Subject (b) (6) – ICF - Subject not consented with the most current IRB ICF within 2 consecutive visits.
3. Subject (b) (6) – Off-schedule procedure - Intensive PK not performed entirely (the 8 hour and 24 hour samples were not collected)
4. Subject (b) (6)
    a. Missing data – HIV-1 RNA and CD4+ samples not collected at 2 or more consecutive visits
    b. Missing data - HIV-1 RNA samples not collected for Weeks 24 and 48 visits after to missed appointments due to COVID-19 travel related restrictions.
5. Subject (b) (6) – Missing data - HIV-1 RNA samples not collected for Weeks 24 and 48 visits after to missed appointments due to COVID-19 travel related restrictions.

6. Subject (b) (6) – ICF - Subject not consented/assented with initial main ICF and sub-study prior to conducting study-related procedures
7. Subject (b) (6) – Off Schedule procedure - Day 1 tests and procedures not completed prior to administration of first dose of study drug: Plasma HIV-1 RNA,. CD4+ cell count, Urine Pregnancy Test, eGFR, AST, ALT, total bilirubin, direct bilirubin.
8. Subject (b) (6) – Other - Any other important protocol deviations that may impact subject safety, well-being or rights (no additional details provided by Applicant).

None of these protocol deviations affected the overall quality or interpretation of the study data.

7.4. Demographic and Baseline Characteristics

A summary of demographic and baseline characteristics for pediatric subjects ≥ 2 years and weighing ≥ 14 to < 25 kg is presented in Table 1. Overall, half the subjects were female (50.0%), and the majority were Black (72.7%), with 22.7% Asian and all were not Hispanic or Latino (100%). They had a median age of 6 years (range: 3 to 9). The mean (range) baseline BMI was 15.6 (range: 12.6, 19.9) kg/m^2 and the median (Q1 = first quartile; Q3 = third quartile) body weight at baseline was 18.7 (15.2, 21.7) kg. All subjects were Tanner stage 1.

Table 1. Demographics and Baseline Characteristics (Cohort 3)

Characteristic	**Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 22)**
Mean Age in years (range) Median Age in years (Q1, Q3)	5 (3, 9) 6 (3, 7)
Sex at birth: Number (%) Male Female	 11 (50.0%) 11 (50.0%)
Race: Number (%) White Black Asian Native Hawaiian or Pacific Islander American Indian or Alaskan Native Other Not Permitted[a]	 0 16 (72.7%) 5 (22.7%) 0 0 1 (4.5%) 0
Ethnicity: Number (%) Hispanic or Latino Not Hispanic or Latino Not Permitted[a]	 0 22 (100%) 0
Baseline Weight (kg) N Mean (range) Median (Q1, Q3)	 22 18.8 (14.1, 24.1) 18.7 (15.2, 21.7)
Baseline Weight Z-score[b] N Mean (range)	 22 -0.65 (-3.15, 1.00)

Median (Q1, Q3)	-0.35 (-1.47, 0.10)
Baseline Height (cm)	
N	22
Mean (range)	109.9 (90, 127)
Median (Q1, Q3)	111.3 (100, 117.5)
Baseline Height Z-score[b]	
N	22
Mean (range)	-0.80 (-3.14, 1.22)
Median (Q1, Q3)	-0.53 (-1.74, 0.00)
Baseline Body Mass Index (kg/m^2)	
N	22
Mean (range)	15.6 (12.6, 19.9)
Median (Q1, Q3)	15.4 (14.3, 16.2)

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-380-1474, Table 16. Page 94-96.
[a] Not Permitted = Local regulators did not allow collection of race or ethnicity information or subject's family preferred not to answer.
[b] Z-scores were generated based on the year 2000 growth charts from the US Centers for Disease Control website

The study enrolled a virologically suppressed, HIV-1 infected population in Cohort 3; thus, all subjects in the Safety Analysis Set in this cohort had baseline plasma HIV-1 RNA < 50 copies/mL (Table 2). The median (Q1, Q3) baseline CD4 cell count was 962 (748, 1419) cells/µL, with 95.5% of subjects having a baseline CD4 cell count ≥ 500 cells/µL. The median (Q1, Q3) baseline CD4% was 32.0% (29.3%, 37.2%).

The median (Q1, Q3) number of years since diagnosis of HIV-1 infection was 4.0 (3.0, 5.0) years. The mode of infection in all subjects was vertical transmission. At baseline, 90.9% of subjects were asymptomatic, 1 subject (4.5%) had symptomatic HIV-1 infection, and 1 subject (4.5%) had a historical diagnosis of AIDS.

All subjects tested negative for HBV and HCV.

Median (Q1, Q3) baseline $eGFR_{Schwartz}$ was 160.5 (145.0, 168.0) mL/min/1.73 m^2.

In accordance with study eligibility criteria, all subjects in Cohort 3 received a regimen containing 2 NRTIs in combination with a third agent prior to the screening visit. Among third agents, 4.5% (1 of 22) of subjects received an INSTI, 50.0% (11 of 22) of subjects received an NNRTI, and 45.5% (10 of 22) of subjects received a PI.

Table 2. Baseline Disease Characteristics (Cohort 3)

Disease Characteristic	**Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 22)**
HIV RNA (Copies/mL)	
< 50	22 (100%)
≥ 50	0
CD4 cell count (µ/L)	
N	22

Mean (range)	1104 (365, 1986)
Median (Q1, Q3)	962 (748, 1419)
CD4 Cell Count Categories (/μL)	
< 50	0
≥ 50 to < 200	0
≥ 200 to < 350	0
≥ 350 to < 500	1 (4.5%)
≥ 500	21 (95.5%)
CD4 Percentage (%)	
N	22
Mean (range)	33.4 (23.8, 46.2)
Median (Q1, Q3)	32.0 (29.3, 37.2)
Years Since Subject Diagnosed with HIV	
N	22
Mean (range)	4.0 (1.0, 9.0)
Median (Q1, Q3)	4.0 (3.0, 5.0)
Mode of Infection	
Vertical transmission	22 (100%)
HIV Disease Status	
Asymptomatic	20 (90.9%)
Symptomatic HIV Infection	1 (4.5%)
AIDS	1 (4.5%)
Estimated Glomerular Filtration Rate by Schwartz Formula (ml/min/1.73 m^2)	
N	22
Mean (range)	157.3 (102, 208)
Median (Q1, Q3)	160.5 (145, 168)

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-380-1474, Table 17. Page 97-98.

7.5. Measurement of Treatment Compliance

The median adherence rates to study drug up to the Week 24 and 48 visits and up to the first data-cut date (June 25, 2020) were 99.4%, 99.5%, and 99.4%, respectively. The percentage of subjects with an adherence rate ≥ 95% was 86.4% up to the Week 24 visit, 83.3% up to the Week 48 visit, and 86.4% up to the data-cut date.

Through the safety update data-cut date (April 9, 2021), the median (Q1, Q3) duration of exposure to the low-dose BVY tablet (B/F/TAF 30/120/15 mg) was 96.1 (70.4, 107.3) weeks.

7.6. Efficacy Results at Week 24 and 48 of Treatment

7.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint was the proportion of subjects with Plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48. At Week 24, 90.9% (20/22) (95% CI: 70.8% to 98.9%) of subjects in Cohort 3 and in the Full Aanalysis Set (FAS) had HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm (Intention To Treat [ITT] Analysis)(Table 3).

At Week 48, 91.7% (11/12) of subjects in Cohort 3 Part A (95% CI: 61.5% to 99.8%) and in the FAS had HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm/ITT analysis (Table 3).

HIV-1 RNA was not collected at Week 24 for 2 subjects and at Week 48 for 1 subject because of COVID-19 pandemic-related study travel disruption.

Table 3. Number and Percentage of Subjects with HIV-1 RNA < 50 Copies/mL by Weeks 24 and 48

	Age ≥ 2 Years and Weight ≥ 14 to < 25 kg	
	Week 24 (N=22)	**Week 48 (N=12)**
HIV-1 RNA < 50 copies/mL (N [%])	20 (90.9%)	11 (91.7%)
95% CI[a]	70.8% to 98.9%	61.5% to 99.8%
No Virologic Data in Week 24 Window	2 (9.1%)	1 (8.3%
Missing Data During Window but on Study Drug	2 (9.1%)	1 (8.3%)

Source: Extracted from Clinical Study Report GS-US-380-1474: Tables 24, page 107; Table 15.9.1.1, page 202; Table 25, page 108; and Table 15.9.1.2., page 203.

[a] The 95% Confidence Intervals (CI) for percentage estimate of HIV-1 RNA < 50 copies/mL were obtained using the Clopper-Pearson Exact method.

Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 Using the Missing = Failure (ITT Analysis) and Missing = Excluded (Per-Protocol Analysis) Imputation Methods

The study demonstrated a high efficacy among those who received treatment, regardless of the method of analysis. By Week 24, 90.9% of subjects achieved the efficacy endpoint when analyzed as originally allocated after randomization, and a 100% of subjects achieved the efficacy endpoint when those with missing data were excluded.

Missing = Failure Method (ITT) Analysis
This analysis includes all patients as originally allocated after randomization, with missing subjects considered to have failed.

- Week 24: 90.9% (20 of 22 subjects); 95% confidence Interval (CI) = 70.8% to 98.9%
- Week 48: 91.7% (11 of 12 subjects); 95% CI = 61.5% to 99.8%

Missing = Excluded (Per-protocol) Analysis
In this analysis, only those subjects who completed the treatment as was originally allocated are included (subjects with missing data are excluded).

- Week 24: 100.0% (20 of 20 subjects); 95% CI = 83.2% to 100.0%.
- Week 48, 100.0% (11 of 11 subjects); 95% CI = 71.5% to 100.0%.

Sensitivity Analysis
A sensitivity analysis was conducted to determine efficacy after excluding the subjects who switched from the low-dose to the adult-dose B/F/TAF tablet after attaining a weight > 25 kg as the study progressed, and the efficacy results were largely unchanged.

7.6.2. Virology Resistance in Cohort 3

Pretreatment genotypic data were available in Cohort 3 for 4 of 22 subjects (18%). One subject had pretreatment M184V and HIV-1 RNA < 50 copies/mL at Week 48. The HIV-1 subtypes present in this group consisted of subtypes B, C, and unknown. No subject had virologic failure and hence none qualified for resistance testing. *Please refer to Section 5. Clinical Microbiology in this review.*

7.6.3. Overall Efficacy Summary

The efficacy of B/F/TAF in children with HIV-1 infection was demonstrated in this open-label, noncomparator trial.

- After 24 weeks of study treatment, the primary efficacy outcome of HIV-1 RNA < 50 copies/mL was attained in 90.9% (20 of 22) subjects, and among those who completed treatment in 100% (20 of 20) subjects. Two subjects were not able to attend their 24 Week visit due to COVID-19 travel restrictions but they were still on study medication.
- Only 12 of 22 subjects had completed 48 Weeks of treatment by the Data-cut date (June 25, 2020). Among those subjects, the primary efficacy outcome of HIV-1 RNA < 50 copies/mL was attained in 91.7% (11 of 12) subjects, and among those who completed treatment in 100% (11 of 11) subjects. One subject was not able to attend their 48 Week visit due to COVID-19 travel restrictions but were still on study medication.

In a sensitivity analysis from which subjects who had switched to the adult-strength B/F/TAF 50/200/25 mg tablet were excluded, the efficacy results were largely unchanged. Mean changes from baseline in CD4 cell count and CD4% by Week 24 and Week 48 were not significantly different from baseline. No subject in Cohort 3 had treatment-emergent resistance to study drug.

8. Safety

Summary
The applicant has submitted safety data from 22 pediatric subjects ≥ 2 years of age (3 to 9 years old) and weighing ≥ 14 to < 25 kg who received at least one dose of B/F/TAF in Trial GS-US-380-1474. The Safety Analysis Set includes 6 subjects who switched to adult-strength B/F/TAF 50/200/25 mg having attained a weight ≥ 25 kg (1 at Week 4, 2 at Week 12, 2 at Week 36, and 1 at Week 60).

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.

On July 1, 2021, the Applicant submitted a 90 Day Safety Update (NDA 210251, SN0118) which provided cumulative data through April 9, 2021. The Safety Analysis Set includes all subjects who had received at least 1 dose of study drug by the data-cut date of 09 April 2021.

Safety analyses plan

A total of 20 subjects from Parts A and B would provide reasonable assessment of safety through Week 48 in children (≥ 2 years of age weighing ≥ 14 to < 25 kg), along with a total of 100 subjects in Cohorts 1 and 2 combined who have contributed to the safety profile of B/F/TAF at exposures predicted to be similar to those of Cohort 3.

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Adverse events described in text were treatment-emergent unless otherwise specified. A treatment-emergent AE was defined as any AE with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug, or any AE leading to premature discontinuation of study drug. Treatment-emergent death referred to a death that occurred between the first and last dose dates (inclusive) of study drug plus 30 days.

AEs were graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life threatening). The number and percentage of subjects with treatment-emergent hepatic events and serious hepatic events by PT was summarized based on the Safety Analysis Set. A listing of hepatic events was provided.

Laboratory data collected during the study were analyzed and summarized for the Safety Analysis Set. Analyses were based on values reported in conventional units.

For selected numeric laboratory tests, values at baseline, each postbaseline analysis window, and change and percentage change (if specified) from baseline at each postbaseline analysis window were summarized using descriptive statistics.

Treatment-emergent laboratory abnormalities were defined as values that increased at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of study drug or the last available date for subjects who were still on study drug at the time of the interim analysis.

Tanner stage assessments were used to evaluate the onset and progression of pubertal changes for subjects ≥ 6 years of age in Cohort 3. Females were rated for pubic hair growth and breast development, and males were rated for pubic hair growth and genitalia development. Tanner stages for breast development and genitalia development at postbaseline visits were summarized by baseline Tanner stage, using frequency count and percentage.

Descriptive statistics were provided for body weight, weight Z-score, height, and height Z-score by cohort and in total. Body weight and weight Z-score, and height and height Z-score were summarized. Vital signs, BMI, and BSA were presented in data listings only.

Palatability and acceptability assessments were summarized by visit using frequency count and percentage, and were listed.

Duration of Treatment

The data-cut occurred after all 22 subjects had completed 24 weeks of treatment. By that time point (June 25, 2020), 12 subjects had also completed 48 weeks of treatment. At the data-cut date (June 25, 2020), the median (Q1, Q3) exposure to study drug was 54.9 (29.3, 66.4) weeks.

This Clinical Study Report summarized the safety data by the data-cut date of June 25, 2020 for all the 22 subjects who completed 24 weeks of treatment and the *90 Day Safety Update provided cumulative data through April 9, 2021.* All subjects who completed the study were included in the safety evaluation.

Safety Data from pediatric and adolescent patients weighing 6 to < 18 years of age, weighing ≥ 25 kg) who received the adult-dose 50/200/25 mg tablet was reviewed and the drug approved for use in this age group on June 18, 2019. *Please refer to Dr. Tanvir Bell's review dated June 6, 2019, for NDA 210251, Supplement 5, SDN 234, sequence number 0050, submitted by the Applicant on December 20, 2018.*

The following is a summary of the assessment of safety for Cohort 3, with 22 subjects ≥ 2 years of age and weighing ≥ 14 to < 25 kg. The Safety Analysis Set includes all subjects who had received at least 1 dose of study drug by the data-cut date of 09 April 2021. The Safety Analysis Set was used for safety analyses and determination of the extent of exposure to study drug, and subject disposition was based on All Screened Subjects.

Adverse events for the sNDA submission at the first cut-date of June 25, 2020, were classified using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 and the AEs for the current safety update report (April 9, 2021) were classified using the MedDRA Version 23.1.

8.1. Adverse Events

Table 4 presents the overall summary of AEs for subjects ≥ 2 years and weighing ≥ 14 to < 25 kg. The majority of subjects (77.3%, 17 of 22 subjects) experienced at least 1 AE, and 13.6% (3 of 22 subjects) had a treatment-related AE. All AEs were Grade 1 (mild) or 2 (moderate) in severity. No subjects experienced Grade 3 or Grade 4 AEs. No subjects had any SAEs, and no subjects had an AE that led to premature discontinuation of study drug. No deaths occurred during the study.

Table 4. Overall Summary of Adverse Events (Safety Analysis Set; Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg) (Safety Analysis Set)

Adverse Events	Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 22)
Any TEAE	17 (77.3%)
Maximum Toxicity Grade	
Grade 1 (mild)	16 (94.2%)
Grade 2 (moderate)	4 (18.2%)
Grade 3 (severe)	0
Grade 4 (life-threatening)	0
Deaths	0
Any SAE	0
Drug-related SAE	0
Drug-related TEAEs	3 (13.6%)
Drug-related Grade 2 TEAE	2 (9.1%)
Drug-related Grade 3 TEAE	0
AE Leading to Premature Discontinuation	0
Any TEAE Hepatic Event*	1 (4.5%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-380-1474: Table 66. Page 155.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
* Grade 1 abnormal feces, not considered related to study drug.

Common Adverse Events

Table 5 presents a summary of treatment-related AEs reported in at least 2 subjects ≥ 2 years and weighing ≥ 14 to < 25 kg, by preferred term. The most commonly reported AEs were Upper Respiratory Tract Infection (22.7%, 5 of 22 subjects), and cough, nasopharyngitis and vomiting (13.6% each, 3 of 22 subjects). Other AEs reported were abdominal pain, constipation, diarrhea, enuresis, headache, nausea, pyrexia, rhonorrhea and viral upper respiratory tract infection (9.1% each, 2 of 22 subjects).

Table 5. Treatment Related Adverse Events in at Least 2 Subjects (Safety Analysis Set; Cohort 3: Age ≥ 2 Years and Weight ≥ 14 to < 25 kg)

Adverse Events	Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 22)
Total # of TEAEs	17 (77.3%)
Upper Respiratory Tract Infection	5 (22.7%)
Cough	3 (13.6%)
Nasopharyngities	3 (13.6%)

Vomiting	3 (13.6%)
Abdominal Pain	2 (9.1%)
Constipation	2 (9.1%)
Diarrhea	2 (9.1%)
Enuresis	2 (9.1%)
Headache	2 (9.1%)
Nausea	2 (9.1%)
Pyrexia	2 (9.1%)
Rhinorrhea	2 (9.1%)
Viral Upper Respiratory Infection	2 (9.1%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-380-1474: Table 67, Page 156.

Adverse Drug Reaction (Related to Study Drug)

Table 6 presents a summary of Adverse Drug Reactions (ADR) reported in > 1 subject ≥ 2 years and weighing ≥ 14 to < 25 kg, by preferred term. Overall, three subjects (13.6%) reported six treatment-related AEs. The most common treatment-related AEs reported for were neutropenia, abdominal pain, constipation, irritability, nausea and social avoidant behavior (4.5% each, 1 of 22 subjects).

Table 6. Study Drug-Related Adverse Events (Safety Analysis Set; Cohort 3: Age ≥ 2 Years of Age and Weight ≥ 14 to< 25 kg)

Adverse Events	Age ≥ 2 Years and Weight ≥ 14 to < 25 kg (N = 22)
Number of Subjects Experiencing Any Treatment Emergent Study Drug-Related Adverse Events	3 (13.6%)
Neutropenia	1 (4.5%)
Abdominal Pain	1 (4.5%)
Constipation	1 (4.5%)
Irritability	1 (4.5%)
Nausea	1 (4.5%)
Social avoidant behavior	1 (4.5%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-380-1474: Table 68, Page 157
Multiple AEs were counted only once per subject per preferred term.
Relatedness to study drug is assessed by the investigator.

Deaths

No Cohort 3 subject died through the safety update data-cut date of April 9, 2021.

Serious Adverse Events (SAEs)

No Cohort 3 subject died through the safety update data-cut date of April 9, 2021.

Discontinuations due to Adverse Events
No subject discontinued study drug or the study due to an AE in Cohort 3 through the data-cut date of April 9, 2021.

Hepatic Adverse Events
One subject had a hepatic AE (Grade 1 abnormal feces) not considered related to study drug.

Laboratory Abnormalities

Change from Baseline in CD4 Cell Counts and Percentages at Weeks 24 and 48
There was a slight non-significant change in CD4 cell counts (mild decrease) and CD4% (mild increase) through Week 48. Mean (SD) CD4 cell counts for Cohort 3 were as follows: at Baseline, 1104 (440) cells/µL; Week 24, 931 (340.3) cells/µL; at Week 48 for Cohort 3, 907 (399.2) cells/µL. Mean (SD) changes from baseline in CD4 cell count were as follows:

- At Week 24: Cohort 3 Parts A and B, –126 (264.2) cells/µL
- At Week 48: Cohort 3 Part A, –22 (184.6) cells/µ

Mean (SD) CD4% for Cohort 3 was as follows: at Baseline, 33.4 (5.97); Week 24, 33.4 (7.56); at Week 48, 32.9 (7.61). Mean (SD) changes from baseline in CD4% were as follows:

- At Week 24: Cohort 3 Parts A and B, 0.2% (4.42%)
- At Week 48: Cohort 3 Part A, –1.1% (3.32%)

Table 7. CD4 Cell Count and Percentage at Baseline, Week 24 and Week 48

	Baseline N=22	**Week 24 (Cohort 3 A, B) N=20/22**	**Week 48 (Cohort 3, A) N=11/12**
CD4 mean (SD)	1104 (440)	931 (340.3)	907 (399.2)
Mean change (SD) from baseline	-	-126 (264.2)	-22 (184.6)
CD4 % mean (SD)	33.4 (5.97)	33.4 (7.56)	32.9 (7.61)
Mean change (SD) from baseline	-	0.2% (4.42%)	-1.1% (3.32%)

Source: Extracted from Clinical Study Report GS-US-380-1474; Table 17, Pages 97-98; and Table 15.9.2.3, Page 223.

Liver-Related Laboratory Parameters
No subject met Hy's Law criteria, defined as concurrent increases in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN with alkaline phosphatase < 2 × ULN and no alternative etiology.

There were no clinically relevant changes from baseline in median values for the liver-related laboratory parameters. There was increased ALT (13.6%, 3 subjects), AST (9.1%, 2 subjects), alkaline phosphatase (18.2%, 4 subjects), or total bilirubin (no subject had an increased total bilirubin) reported at Week 24 or 48. The majority of liver-related laboratory abnormalities were Grade 1; 1 subject had a Grade 3 laboratory abnormality of increased alkaline phosphatase at Week 48 that resolved by Week 60 (Subject # (b) (6)). There were no Grade 4 liver-related laboratory abnormalities reported.

Metabolic Laboratory Parameters

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol:HDL cholesterol ratio, triglycerides, or glucose at Weeks 24 or 48.

Graded abnormalities were reported for fasting total cholesterol (hypercholesterolemia, 14.3%, 3 of 21 subjects), fasting LDL cholesterol (increased, 9.5%, 2 of 21 subjects), and glucose (fasting hyperglycemia, 18.2%, 4 of 22 subjects; fasting hypoglycemia, 4.5%, 1 of 22 subjects). All graded fasting lipid and glucose abnormalities were Grade 1.

Renal Laboratory Parameters

Serum Creatinine

Increases from baseline in median values for serum creatinine were observed at Week 4, and stabilized after Week 8. The median (Q1, Q3) baseline serum creatinine value was 0.38 (0.34, 0.43) mg/dL. The median (Q1, Q3) changes from baseline in serum creatinine at Weeks 24 and 48 were 0.07 (0.02, 0.09) and 0.06 (0.03, 0.15) mg/dL, respectively. A graded laboratory abnormality in serum creatinine was reported for 1 subject (4.5%, 1 of 22 subjects). This subject had a transient Grade 4 elevated serum creatinine that resolved 4 days later (Subject # 07409-7301).

Estimated Glomerular Filtration Rate

Corresponding to the results for serum creatinine, decreases from baseline in median values for $eGFR_{Schwartz}$ were observed at Week 1, stabilizing after Week 16. The median (Q1, Q3) baseline $eGFR_{Schwartz}$ value was 160.5 (145.0, 168.0) mL/min/1.73 m^2. The median (Q1, Q3) changes from baseline in $eGFR_{Schwartz}$ at Weeks 24 and 48 were −19.0 (−24.0, 4.0) and −8.0 (−38.0, −2.0) mL/min/1.73 m^2, respectively.

Relevant Summary of Clinical Laboratory Abnormalities

Most subjects (95.5%; 21 of 22) had at least 1 laboratory abnormality. The maximum toxicity was Grade 1 or 2 for 77.3% of subjects; Grade 3 or 4 laboratory abnormalities were reported for 18.2% of subjects. The most common Grade 3 or 4 laboratory abnormality was decreased neutrophils (13.6%, 3 of 22 subjects) in the following subjects as follows:

- Subject # (b) (6) (7 year old male), Grade 3 at Week 24, Grade 1 by Week 36, Grade 0 by Week 48
- Subject (b) (6) (3 year old female), Grade 4 at Week 1 then Grade 0 by Week 2.
- Subject # (b) (6) (9 year old female), Grade 3 at Week 36 to Grade 0 by Week 48.

As mentioned in the Liver-Related Laboratory Parameters above, 1 subject had a Grade 3 laboratory abnormality of increased alkaline phosphatase at Week 48 that resolved by Week 60 (Subject # (b) (6)). Also, as mentioned above in Renal Laboratory Parameters, Subject # (b) (6) had a serum creatinine value of 7.11 mg/dL (Grade 4) at Week 60 that dropped to 0.57 mg/dL 4 days later (Grade 0).

There was a small change in CD4 cell counts (mild decrease) and CD4% (mild increase) through Week 48 that was not considered clinically significant. The mean change from baseline to Week 24 in CD4+ cell count (SD) was −126 (264.2) cells per mm^3; and the mean change in CD4% (SD) from baseline to Week 24 was 0.2% (4.4%).

Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no clinically relevant changes in any vital signs parameter in any subject.

Body Weight and Height
Body weight and weight Z-scores, and body height and height Z-scores for subjects in the Safety Analysis Set are presented below.

Body Weight
Median (Q1, Q3) body weight at baseline and Week 48 was 18.7 (15.2, 21.7) kg and 22.3 (17.4,
25.0) kg, respectively. At baseline, the body weight Z-score was mean (SD) -0.65 (1.073); median (Q1, Q3) -0.35 (-1.47, 0.10). Body weight Z-scores increased during the study. The change from baseline at Week 48 was mean (SD) 0.09 (0.357); median (Q1, Q3) 0.13 (-0.22, 0.39).

Height
Median (Q1, Q3) height at baseline and Week 48 was 111.3 (100.0, 117.5) cm and 119.5 (106.4, 129.6) cm, respectively. At baseline, the height Z-score was mean (SD) -0.80 (1.118); median (Q1, Q3) -0.53 (-1.74, 0.00). There were no clinically relevant changes in height Z-scores. The change from baseline at Week 48 was mean (SD) 0.16 (0.366); median (Q1, Q3) 0.14 (-0.20, 0.50).

Tanner Stage Assessments
For subjects ≥ 6 years of age in Cohort 3 (not evaluated for those < 6 years), Tanner stages for genitalia in males and breasts in females from baseline to Weeks 24 and 48 remained at Tanner stage which is consistent with this pediatric study population.

SUMMARY OF SAFETY (Cohort 3)
Overall, low-dose B/F/TAF was well tolerated by children in Cohort 3 through a median duration of exposure of 54.9 weeks.

Overall, 77.3% (17 of 22) of subjects had at least 1 AE. The most commonly reported AEs were upper respiratory tract infection (22.7%, 5 subjects); and cough, nasopharyngitis, and vomiting (13.6%, 3 subjects, each). The majority of AEs reported were Grade 1. No Grade 3 or 4 AEs were reported. Adverse events considered related to study drug were reported for 13.6% (3 of 22) of subjects. Among study drug-related AEs, none was reported with greater frequency than single subject incidence. There were no treatment-emergent deaths or SAEs reported. No subject discontinued study drug or the study due to an AE. No pregnancies were reported.

One subject had a hepatic AE reported (Grade 1 abnormal feces) that was not considered related to study drug. There were no clinically relevant changes from baseline in median values for the liver-related laboratory parameters ALT, AST, alkaline phosphatase, or total bilirubin at Week 24 or 48. No subject met Hy's Law criteria.

There were no clinically relevant changes from baseline in mean values for CD4 count or CD4 percentage, or median values forhematology or clinical chemistry (including metabolic) parameters, and median values were within the relevant reference ranges. Most subjects (95.5%, 21 of 22) had at least 1 laboratory abnormality. Grade 1 or 2 laboratory abnormalities were reported for 77.3% of subjects; Grade 3 or 4 laboratory abnormalities were reported for 18.2% of subjects, all of which resolved without intervention.

There were no clinically relevant changes from baseline in vital signs parameters, height or Tanner stage. Body weight Z-scores increased during the study with a change from baseline at Week 48 of mean (SD) 0.09 (0.357); median (Q1, Q3) 0.13 (-0.22, 0.39).

The overall safety profile of B/F/TAF as presented by the Applicant in the 90 Day Safety Update (data-cut April 9, 2021) remained consistent with that described in the initial sNDA submission at the date-cut of June 25, 2020, and there are no new safety concerns.

8.2. Special Populations

The pediatric HIV-infected subjects evaluated in Study GS-US-380-1474 represent a special patient population. A subsequent trial is planned to evaluate the PK, safety and efficacy of B/F/TAF in pediatric subjects weighing less than 14 kg.

8.3. Drug Interactions

No new findings relevant to the coadministration of B/F/TAF with other drugs are submitted with this update to the marketing application.

8.4. Use in Pregnancy and Lactation

N/A for this submission.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA application. No significant issues were raised to warrant a public discussion.

10. Pediatrics

This submission and review of the application is to support use of B/F/TAF in pediatric patients weighing ≥ 14 and <25kg. The study was reviewed by the Pediatric Review Committee (PeRC) and they agreed with our approval determination and that the PMR for the study (#3322-1) for ages 2 to <18 years old is considered fulfilled. They also agreed that for children who cannot swallow the low-dose tablet whole, the tablet can be split and all parts are to be ingested within 10 minutes, since this will provide maximum flexibility for dosing in younger children until an age-appropriate formulation currently being developed for use in patients weighing <14 kg is available.

11. Other Relevant Regulatory Issues

11.1. Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was well organized and reasonable to navigate. The Division did not consult the Office of Scientific Investigations (OSI) for clinical inspection of the trial sites due to the following reasons:

- There is no site that enrolled a disproportionately large number of cases compared to the rest that would affect the outcome of the study. 22 subjects were enrolled at 7 South Africa sites (n=11); 4 US sites (n=4); 2 Thailand sites (n=5) and 1 Ugandan site (n=2) Each site enrolled 1-2 subjects except for Site #07456 (Thailand) that enrolled 4, and Site #015551 (South Africa) that enrolled 3.

- There were few reported protocol deviations, most of which were related to missed appointments, lab work or signing of updated ICFs, due to COVID-19 related travel restrictions. None of these protocol deviations affected the overall quality or interpretation of the study data (see Section 7.3 Protocol Deviations).

A Biopharmaceutical inspection was requested for a routine inspection one of their Central Laboratory ((b) (4)). The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that no inspection was needed since OSIS inspected the site in (b) (4) , which falls within the surveillance interval. The prior inspection was conducted under the following submissions: Non Responsive

11.2. Compliance with Good Clinical Practices

As per the Sponsor, the clinical study included in this submission (Study GS-US-380-1474) is being conducted under a US investigational new drug application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) guideline for Good Clinical Practice (GCP) (Sections 7.5, 8.1.2, and 8.2.2), and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC, as well as other local legislation.

The protocol, protocol amendments, consent forms, and administrative letters were submitted by each investigator to a duly constituted independent ethics committee (IEC) or institutional review board (IRB) for review and approval before study initiation. Protocol amendments and all revisions to the consent form after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. Copies of all IEC/IRB approval letters are maintained in the trial master file.

11.3. Financial Disclosures

Gilead Sciences has submitted Form FDA 3454, which certifies that they (Applicant) did not enter into any financial relationships with principle or sub-investigators. The form included an attachment containing the names of principal investigators and sub-investigators for study GS-US-380-1474 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3). There were a total of 113 investigators (26 Principal Investigators and 87 Sub-Investigators), all of whom certified that they have no disclosable financial interests, except for one investigator who certified having received "Significant payment of sorts ≥ $25,000" for whom Forms FDA 3455 and Minimization of Bias Form were submitted and are acceptable. The one investigator who had financial interests or arrangements with the Sponsor, represented (b) (6) % of all investigators and was at one site which enrolled only (b) (4) patients or (b) (4) % (b) (4) /113) of all patients enrolled in the study, neither of which was in Cohort 3 (the (b) (4) children were (b) (4) years old). None of the investigators are Gilead employees. See Appendix 2 for the Clinical Investigator Financial Disclosure Review.

11. Labeling

The USPI (United States Prescribing Information) and PPI (Patient Package Insert) have been agreed to and are summarized below.

Please note that the numbering in this section is that of the label only and is different than the numbering in the rest of this review.

The labeling has been updated to reflect changes in the indication, extending the population to pediatric patients weighing at least 14 kg to less than 25 kg, using the low-dose tablet of 30 mg bictegravir, 120 mg emtricibine and 15 mg of tenofovir alafenamide, taken once daily with or without food.

The changes with this efficacy supplement primarily affected the following sections. These changes were accepted by Gilead.

HIGHLIGHTS OF PRESCRIBING INFORMATION

This section was updated to reflect the changes made to the label as described below. The blue font indicates additions and the blue font with strikethrough indicates the deletions.

1 INDICATIONS AND USAGE

This section was updated as follows:

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients (b) (4) 14 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 with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

Rationale # 1: (b) (4) *was removed from the indication statement and the sections in the label that describe dosage and use. This decision was based on the fact that:*

- (b) (4)

Given that the main determinant in using the low-dose tablet was the weight range of > 14 kg to < 25 kg (b) (4) *was removed throughout the label in any section describing the recommended dosage or usage.* (b) (4) .

2 DOSAGE AND ADMINISTRATION

2.3 Recommended Dosage in Pediatric Patients [redacted] Weighing at Least 14 kg to Less than 25 kg

The recommended dosage of BIKTARVY is one tablet containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF taken orally once daily with or without food in:

- pediatric patients [redacted] weighing at least 14 kg to less than 25 kg, with an estimated creatinine clearance greater than or equal to 30 mL [redacted]/min *[see Use in Specific Populations (8.4, 8.6) and Clinical Pharmacology (12.3)]*.

For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes.

See Rationale #1 above for the deletion of [redacted]

Rationale # 2: *The addition of language regarding splitting the tablet was based on the following. Given that no children younger than 3 years of age were enrolled, there was a concern regarding the tolerability and compliance of 2 year old children to swallow the low-dose tablet (14 x 6.5 mm) given that it was almost the same size the adult-dose tablet (15 x 8 mm). Given this concern, the division asked the Applicant to provide publications or data that children as young as 2 years of age were able to swallow the low-dose Biktarvy tablet or similar tablets on a daily basis to support chronic administration.*

- *The Applicant acknowledged the paucity of studies describing the ability of children to swallow the same size tablets. They noted that :*
  - *In one literature review, {Punam Ministry 2016}, tablets up to 8 mm in diameter were demonstrated to be acceptable (able to be swallowed whole) in children as young as 2 years of age.*
  - *In one of the studies included in this review, children aged 2 to 18 years old took up to 7 tablets ranging in size from 5 mm to 8 mm, depending on the size each child was able to swallow, every other day for 1 year {Kreeftmeijer-Vegter 2013}. Among the 46 children aged 2 to 5 years, 41% received 7 or 8 mm tablets including 2 children aged 2 years treated with 7 mm diameter tablets, ie, tablets similar in size to the B/F/TAF low dose tablet.*
  - *Van Reit-Nales et. al. evaluated 10 Pediatric Investigational Plans (PIPs) {van Riet-Nales 2014}, which showed that they included medium size (5 – 9 mm), immediate release or film coated tablets and that in 2 agreed PIPs they included tablets ≥ 10 mm for children 2 – 5 years of age.*
  - *Furthermore, in this study (GS-US-380-1474), among the 6 children who were 3 years of age at enrollment, 2 children were able to swallow the low-dose tablet whole, 2 children split the tablet into two parts and swallowed both parts within 10 minutes, and 2 children initially split the tablet but later were able to swallow the tablet whole. Of the four who split the tablet, they all rated the split tablet as "okay" in size, and the whole tablet as too big at least on one occasion.*
- *The Division also discussed the bioavailabity of the split tablet compared to the whole tablet by consulting:*

- *Chemistry, Manufacturing and Controls (CMC): As per an email communication from Dr. David Lewis dated July 26, 2021, the Applicant does not have to provide information concerning the equivalency of two split portions of a tablet (content, dissolution, loss of mass), because the patient is to be administered ALL of the portions of the tablet (within 10 minutes as described)*
- *Division of Biopharmaceutics: As per an email communication from Dr. Kevin Wei dated July 29, 2021, the proposed product is formulated as immediate release monolayer tablets without functional film coat, and hence there is no concern on breaking/cutting/chewing on the tablet (in any number and shape of pieces) before swallowing, as long as all pieces of the whole tablet are administrated at the same time or within a short period of time.*
- *Division of Pediatric and Maternal Health (DPMH): As per an email communication from Dr. Ndidi Nworkorie dated July 29, 2021, they reviewed 5 NDA applications for other pediatric drugs with language in labeling addressing solid oral dosage form in pediatric patients. Two of these applications had specific instructions to swallow the tablet whole and not to chew or crush. Given the feedback from CMC, DPMH agrees that we can add language to the label specifying that if the child is unable to swallow the tablet whole then the tablet may be split and administered within 10 minutes.*

- *Given that data was available from this study (GS-US-380-1474) included subjects that split the tablet and ingested all parts within 10 minutes, then a statement to that effect was added in Section 2.3 and Section 17, and in the "Patient Information" section.*

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. Dolutegravir, another integrase inhibitor, has been associated with neural tube defects (NTDs) *(see Data)*. Discuss the benefit-risk of using BIKTARVY with individuals of childbearing potential, particularly if pregnancy is being planned. (b) (4)
BIKTARVY use in women during pregnancy has (b) (4) has been evaluated in a limited number of women reported to the APR; consequently, there are insufficient BIC data from the APR to adequately assess the risk of major birth defects. Reports of pregnant individuals treated with other drug products containing TAF or FTC contribute to APR's overall risk assessment for these components. (b) (4)
Available data from the APR show no statistically significant difference in the overall risk of major birth defects for FTC or TAF compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15-20%. (b) (4)

[redacted]

Data

Human Data

Prospective reports from the APR of overall major birth defects in pregnancies exposed to the components of BIKTARVY are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area,and does not include outcomes for births that occurred at less than 20 weeks gestation.

Bictegravir (BIC):

Data from an observational study in Botswana showed that dolutegravir, another integrase inhibitor, was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. Data available to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address this risk with BIC.

There are an insufficient number of reports to the APR to adequately assess the risk of major birth defects associated with BIC exposure. The APR has received prospective reports of 3 birth defects among 100 (3.0%) first trimester exposures to BIC-containing regimens during pregnancy resulting in live births. No birth defects were reported among 40 exposures during the second/third trimester.

Emtricitabine (FTC):

Based on prospective reports to the APR of [redacted] over 5,400 exposures to FTC-containing regimens during pregnancy resulting in live births (including over 3,900 [redacted] exposed in the first trimester and over 1,500 ~~1,080~~ exposed in the second/third trimester), [redacted] the prevalence of birth defects in live births was 2.6% [redacted] (95% CI: 2.2% to 3.2%) [redacted] and 2.7% (95% CI: 1.9% to 3.7%) [redacted] following first and second/third trimester exposure, respectively, to FTC-containing regimens.

Tenofovir Alafenamide (TAF):

Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to

TAF-containing regimens.

Rationale # 3: *The Applicant submitted additional changes to the label from NDA 210251, supplement 013 (approved September 10, 2021) regarding updated information related to reports of birth defects from pregnant individuals treated with Biktarvy components (TAF and FTC).*

8.4 Pediatric Use

The safety and effectiveness of BIKTARVY have been established as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection (b) (4) in pediatric patients weighing at least ~~2 years~~14 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 with no history of (b) (4) treatment failure and (b) (4) no known substitutions associated with resistance to the individual components of BIKTARVY *[see Indications and Usage (1) and Dosage and Administration (2.2, 2.3)]*.

Use of BIKTARVY in pediatric patients (b) (4) weighing at least 14 kg is supported by the following:

- trials in adults *[see Clinical Studies (14.1)]*
- an open-label trial in three age-based cohorts of virologically-suppressed pediatric subjects *[see Clinical Studies (14.4)]*
    - Cohort 1: 12 to less than 18 years of age and weighing at least 35 kg receiving BIKTARVY through Week 48 ((b) (4) N=50), (b) (4)
    - Cohort 2: 6 to less than 12 years of age and weighing at least 25 kg receiving BIKTARVY through Week 24 ((b) (4) N=50), (b) (4)
    - Cohort 3: at least 2 years of age and weighing at least 14 to less than 25 kg through Week 24 ((b) (4) , N=22). No pediatric subjects 2 years of age were enrolled; of the 6 pediatric subjects who were 3 years of age at enrollment, 3 subjects weighed between 14 to less than 15 kg.

The safety and efficacy of BIKTARVY in these pediatric subjects (b) (4) were similar to that in adults, and there was no clinically significant change in exposure for the components of BIKTARVY *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4)]*.

Safety and effectiveness of BIKTARVY in pediatric patients (b) (4) weighing less than 14 kg have not been established.

Rationale # 4: *Given that this supplemental NDA is focused solely on Study number 1474 (GS-US-380-1474),* (b) (4).

14.2 Clinical Trial Results in Adults with HIV-1 and (b) (4) No Antiretroviral Treatment History

In Trial 1489, [redacted] adults were randomized in a 1:1 ratio to receive either BIKTARVY (containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF) (N=314) or ABC/DTG/3TC (600 mg/50 mg/300 mg) (N=315) once daily. In Trial 1490, subjects were randomized in a 1:1 ratio to receive either BIKTARVY (N=320) or DTG + FTC/TAF (50 mg + 200 mg/25 mg) (N=325) once daily.

Rationale # 5: *The text was revised to specify that these results are in adults using the adult dose. When it was first written the pediatric data and the low dose tablet were not yet available. Similar changes were made to* ***Section 14.3 and 14.4*** *(not shown here).*

14.4 Clinical Trial Results in [redacted] Pediatric Subjects with HIV-1

The following changes were made in the last paragraph:

Cohort 3: Virologically-suppressed children (at least 2 years; at least 14 to less than 25 kg)

Subjects in cohort 3 treated with BIKTARVY (containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF) once daily had a mean age of 5 years (range: 3 to 9) and a mean baseline weight of 18.8 kg (range: 14 to 24), 50% were female, 23% were Asian and 73% were black. At baseline, [redacted] the mean CD4+ cell count (SD) was [redacted] 1104 (440), and [redacted] the mean CD4% (SD) was [redacted] 33.4% (6.0%).

After switching to BIKTARVY, 91% (20/22) of [redacted] subjects in cohort 3 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. HIV-1 RNA was not collected at Week 24 for 2 subjects because of COVID-19 pandemic-related study disruption. The mean change from baseline to Week 24 in CD4+ cell count ~~at Week 24~~(SD) was −126 (264.2) cells per mm^3 ; and the mean change in CD4% (SD) from baseline to Week 24 was 0.2% (4.4%).

Rationale # 6: *The Applicant had described the CD4 cell count and CD4% at baseline as a* [redacted] *and then in the next paragraph described the change from baseline as a mean (SD). Furthermore, the Applicant only provided the mean change from baseline in CD4 count, but not the CD4%. To allow for meaningful interpretation, the text was revised to provide mean (SD) baseline CD4 count and CD4%* [redacted] *and the mean change(SD) from baseline in both CD4 cell count and CD4%.*

16 HOW SUPPLIED/STORAGE AND HANDLING

BIKTARVY tablets are available in bottles and blister packs:

Bottle

- 50 mg/200 mg/25 mg tablets each contain 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). These tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side (NDC 61958-2501-1).
- 30 mg/120 mg/15 mg tablets each contain 30 mg of BIC,120 mg of FTC, and 15 mg of TAF. These tablets are pink, capsule-shaped, and film-coated with “GSI” debossed on one side and “B” on the other side (NDC 61958-2505-1).

Each bottle contains 30 tablets with a silica gel desiccant, polyester coil, and child-resistant closure as follows

Store bottle below 30 °C (86 °F).

Keep ~~container~~ bottle tightly closed.

Dispense only in original containers

Blister Pack

- 50 mg/200 mg/25 mg tablets each contain 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF. These tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side (NDC 61958-2501-3).

Each blister pack contains 30 tablets (4 strips each containing 7 tablets and 1 strip containing 2 tablets). Blister packs are sealed with a child-resistant laminated foil lidding material (peel-push), and each blister cavity contains a die-cut desiccant film which is heat staked to the foil lidding material.

Store blister pack at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

Rationale # 7: *The Applicant submitted additional changes to the label from NDA 210251, supplement 012 (approved by CMC on August 24, 2021) to add a 30 count blister pack configuration.*

17 PATIENT COUNSELING INFORMATION

The following text was added:

Tablet Splitting

Advise caregivers that, for children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes *[see Dosage and Administration (2.3)]*.

See Rationale # 2 above.

Patient Information

The following subsections in “Patient Information” handout were revised for consistency with changes made in the Full Prescribing Information (FPI) mentioned above.

What is BIKTARVY?

- The phrase [redacted] (b) (4) was deleted

How should I take BIKTARVY?

The following sentence was added:

- For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes.

How should I store BIKTARVY?

- Store BIKTARVY bottle below 86 °F (30 °C).
- Keep the bottle tightly closed.
- Store BIKTARVY blister pack at room temperature between 68 °F to 77 °F (20 °C to 25 °C).
- Keep BIKTARVY in its original bottle or blister pack.

Keep BIKTARVY and all medicines out of reach of children.

See Rationale # 1, Rationale # 2 and Rationale # 7 above.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No recommendation for a REMS is indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are indicated.

13. Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

14. References

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Appendix 1

Patient Experience Data for Epclusa in children ≥ 2 years old and weighing ≥ 14kg to < 25 kg with HIV-1 infection were collected within the clinical trials. The following is a summary of the data collected in this study (GS-US-380-1474).

Palatability and acceptability of the low-dose B/F/TAF 30/120/15 mg tablet

In the following summary of the palatability and acceptability of the low-dose B/F/TAF 30/120/15 mg tablet, responses from subjects who had switched to the adult-strength B/F/TAF 50/200/25 mg tablet having attained a weight ≥ 25 kg (1 subject at the Week 4 assessment; 4 subjects at the Week 48 assessment) are excluded.

In Cohort 3, the majority of subjects had a neutral ("maybe good or maybe bad/could not taste it") or positive ("good" or "super good") palatability assessment at baseline (90.9%, 20 of 22 subjects) and Week 24 (89.5%, 17 of 19 subjects).

The majority of subjects had a neutral or positive acceptability response for ease of swallowing, shape, and size when the study drug was swallowed whole at baseline, Weeks 4, 24, and 48:

- In response to the question "How easy was it to swallow the study drug?", the majority of subjects who swallowed the study drug whole reported "easy" or "super easy" (baseline: 82.4%, 14 of 17 subjects; Week 4: 87.5%, 14 of 16 subjects; Week 24: 75.0%, 12 of 16 subjects; Week 48: 71.4%, 5 of 7 subjects).
- In response to the question "How did the shape of the study drug feel when you swallowed it?", the majority of subjects who swallowed the study drug whole reported "good" or "super good" (baseline: 75.0%, 12 of 16 subjects; Week 4: 93.3%, 14 of 15 subjects; Week 24: 75.0%, 12 of 16 subjects; Week 48: 57.1%, 4 of 7 subjects).
- In response to the question "How did the size of the study drug feel when you swallowed it?", the majority of subjects who swallowed the study drug whole reported "okay" (baseline: 88.2%, 15 of 17 subjects; Week 4: 86.7%, 13 of 15 subjects; Week 24: 81.3%, 13 of 16 subjects; Week 48: 71.4%, 5 of 7 subjects).

For those subjects who split the drug in half, all reported taking each half within 10 minutes (5 subjects each at baseline and Week 4, 3 subjects at Week 24, and 1 subject at Week 48). Detailed responses to the acceptability questionnaire are summarized in the Clinical Study Report (Table req12896.3, pages 527-8; and Table req 12896.4, pages 529-535).

The following labeling changes were made based on this data:

- The following sentence was added in Sections 2.3:

For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes.

- The following sentence was added in Section 17 under "Patient Information":

Advise caregivers that, for children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are ingested within approximately 10 minutes *[see Dosage and Administration (2.3)]*.

Appendix 2

Clinical Investigator Financial Disclosure Review

Application Number: NDA 212051

Submission Date(s): April 9, 2021

Applicant: Gilead Sciences, Inc.

Product: BIKTARVY® (bictegravir/emtricitabine/tenofovir alafenamide; B/F/TAF)

Reviewer: Samer El-Kamary, MD, MPH

Date of Review: August 31, 2021

Covered Clinical Study (Name and/or Number):
"A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Adolescents and Children" (Study Number: GS-US-380-1474 [Cohort 3])

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 113 (26 Principal Investigators and 87 Sub-Investigators)		
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): 1		
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: 1 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:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The Sponsor adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for Industry, Financial Disclosure by Clinical Investigators, and by 21 CFR 54.4.

None of the 113 Investigators for Study GS-US-380-1474 are employed by the Sponsor. One of the investigators, representing (b) (6)% (b) (6)/113) of the total number of investigators, have disclosable financial interests/arrangements which the Sponsor defined as 'Significant payment of other sorts > $25,000' for whom forms FDA 3455 and Minimization of Bias Form were submitted and are acceptable.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint includes PK parameters and the viral load assessed at Week 24, which are objective laboratory measurements that are assessed at a separate central laboratory ((b) (4)) and not vulnerable to investigator bias, or other members of the site staff. While the AE assessment is performed by the investigators and their staff in this open-label study, the Sponsor states that 100% of the source documents will be verified by a Clinical research Associate (CRA) working on behalf of the Applicant. The CRA is then able to evaluate whether the investigator is under-reporting or over-reporting the incidence of AEs, and any discrepancy will be reported promptly to the Applicant.

Hence, the fact that the main laboratory efficacy endpoints are objectively measured by a third party laboratory and that the CRA monitor reviews the patient's source documents would minimize the potential for investigator bias to play a role. Finally, the one investigator who had financial interests or arrangements with the Sponsor, represent (b) (6)% of all investigators and is at one site which enrolled only (b) (6) patients or (b) (6)% (b) (6)/113) of all patients enrolled in the study, neither of which was in Cohort 3 (the (b) (6) children were (b) (6) years old). In conclusion, the likelihood that the trial results were biased based on financial interests is minimal overall, and unlikely for Cohort 3 in particular, and should not affect the approvability of the application.

See https://www.fda.gov/media/85293/download

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/s/

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