sNDA 210251/S-5
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Clinical and Cross-Discipline Team Leader Summary Review

Date	May 11, 2019
From	Tanvir Bell, MD - Clinical Reviewer Wendy Carter, DO - CDTL
Subject	Summary Clinical Review
NDA/BLA # and Supplement#	NDA 210251 – Supplement 5 (SDN 234)
Applicant	Gilead Sciences, Inc.
Date of Submission	December 20, 2018
PDUFA Goal Date	June 20, 2019
Proprietary Name	BIKTARVY®
Established or Proper Name	Bictegravir (BIC, B)/emtricitabine (FTC, F) /tenofovir alafenamide (TAF)
Dosage Form(s)	B/F/TAF 50/200/25 mg fixed-dose combination (FDC)
Applicant Proposed Indication(s)/Population(s)	HIV-1 infected, virologically suppressed adolescents and children
Applicant Proposed Dosing Regimen(s)	B/F/TAF 50/200/25 mg
Recommendation on Regulatory Action	*Approval*

1. Benefit-Risk Assessment

This review summarizes the data and main review issues for Gilead's sNDA 210251 Supplement 5 seeking approval for Bictegravir (BIC, B)/emtricitabine (FTC, F) /tenofovir alafenamide (TAF) 50/200/25 mg in pediatric patients weighing ≥ 25 kg. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data. B/F/TAF tablet formulation was approved on February 7, 2018 based on review of Phase 3 data from two trials in treatment naïve HIV-1 infected subjects (Trials 1489 and 1490) and two trials in virologically suppressed subjects (Trials 1848 and 1888). The current indication for B/F/TAF is use as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of B/F/TAF in antiretroviral naïve and virologically suppressed adults.

This supplement (S5) was granted a priority review for several reasons. The data in the application are in response to post-marketing requirements (PMR) issued under the Pediatric Research Equity Act (PREA) for B/F/TAF. In addition, the application for B/F/TAF allows for the

use of a fixed dose combination (FDC) taken once daily in the pediatric population, which will provide an additional single tablet regimen for the HIV-1 infected patient population weighing at least 25 kg.

As part of this submission, Gilead also submitted further drug-drug interaction analyses to support revisions to labeling recommendations pertaining to the coadministration of Biktarvy (BVY) with polyvalent cation (PVC)-containing antacids/supplements.

Based on review of the safety and efficacy data submitted in this sNDA, we recommend approval of B/F/TAF in virologically suppressed pediatric patients weighing at least 25 kg.

Details for the original NDA application for B/F/TAF can be found in the Unireview (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210251Orig1s000MultidisciplineR.pdf) The currently approved label is available at (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf).

A benefit risk summary and assessment follow.

Benefit-Risk Summary and Assessment

Bictegravir (BIC) inhibits the strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Bictegravir is co-formulated in a fixed dose combination (FDC) pill with emtricitabine (FTC) and tenofovir alafenamide (TAF), two approved nucleos(t)ide reverse transcriptase inhibitors (NRTIs) of the HIV-1 virus. B/F/TAF (BIKTARVY®) is approved as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed on a stable antiretroviral regimen with no known substitutions associated with resistance to the individual components.

As reported by the CDC, the estimated incidence of new HIV-1 diagnoses in the US in 2017 was 38,739 among adults and children[1]. The goal of HIV treatment is to durably suppress plasma HIV RNA, preserve and restore the immune system, and reduce HIV-associated morbidity. INSTIs in combination with two NRTIs have become a preferred component of HIV treatment as recommended by the HIV treatment guidelines[2,3]. Data from open label single arm trial, Trial 1474, virologically suppressed adolescents 12 to 18 years of age weighing ≥ 35 kg (Week 48 for Cohorts 1A and 1B) and children 6 to < 12 years of age, weighing ≥ 25 kg (Week 48 for Cohort 2A and Week 24 for Cohort 2B) were submitted in this supplement.

The 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in patients relative to adults were outside the pre-defined no effect boundaries (70-143%). However, the observed differences are not considered clinically significant based on the exposure-response relationships. Additionally, both the efficacy and safety observed in the pediatric cohorts were consistent with, and similar to that observed in the adult population. The proportion of subjects with plasma viral load < 50 copies/mL at Week 48 (based on FDA snapshot algorithm) for Cohort 1 was 98% (49/50), and the proportion of subjects with plasma viral load < 50 copies/mL at Week 24 for Cohort 2 was 100% (50/50). Subjects tolerated B/F/TAF well, with a discontinuation rate due to adverse events of 1%. The adverse reaction occurring in at least two percent of subjects was abdominal pain. No new adverse reactions or Grade 3 or 4 laboratory elevations were identified that are not already included in the label.

In conclusion, approval of B/F/TAF for pediatric patients weighing at least 25 kg is fully supported by available evidence and analysis of pharmacokinetics, efficacy, and safety results from Trial 1474.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The estimated incidence of new HIV-1 diagnoses in the US in 2017 was 38,739 among adults and children.[1] • The goal of HIV treatment is to durably sustain plasma HIV RNA suppression, preserve and restore the immune system, and reduce HIV-associated morbidity.	If untreated, HIV is a life-threatening condition, one that affects a large population. Potential consequences of untreated HIV are morbidity and mortality. HIV infection is a significant public health concern.
Current Treatment Options	• INSTIs in combination with two NRTIs have become a preferred component of HIV treatment as recommended by the pediatric as well as the adult and adolescent DHHS HIV treatment guidelines.[2,3] • HIV therapy is often lifelong. • FDCs are convenient options for treatment. • Adolescents have many FDC options available, including complete single tablet regimens (STR); however, in those weighing less than 40 kg there are fewer FDC or STR options. • Elvitegravir(E)/cobicistat(C)/ emtricitabine (F)/tenofovir alafenamide (TAF) and E/C/F/tenofovir disoproxil fumarate (TDF) are STR options for pediatric patients down to 25 kg and 35 kg, respectively. Cobicistat is associated with drug-drug interactions.	The HIV treatment armamentarium for pediatric patients would benefit from another FDC complete regimen treatment option, particularly for those in lower weight bands. In addition, the lack of cobicistat decreases the number of drug-drug interactions that may complicate treatment.
Benefit	• The 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in patients relative to adults were outside the pre-defined no effect boundaries (70-143%). However, the observed differences are not considered clinically significant based on the exposure-response relationships. • The efficacy in HIV-1 virologically suppressed pediatric patients was established in open labeled trial with plasma viral load < 50 copies/mL at 48 weeks for Cohort 1 and 24 weeks for Cohort 2. The proportion of subjects with plasma viral load < 50 copies/mL at Week 48 in Cohort 1	Exposures of B/F/TAF components and tenofovir, a prodrug of TAF, in trial subjects were considered acceptable from a PK and PD standpoint. B/F/TAF provided durable virologic suppression in this pediatric population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and was 98% (49/50), and the proportion of subjects with plasma viral load < 50 copies/mL at Week 24 for Cohort 2 was 100% (50/50). Overall, less than two percent of subjects experienced virologic failure on B/F/TAF at Weeks 24 or 48. • Some INSTIs, including bictegravir and dolutegravir, can have a high genetic barrier to resistance. • Bictegravir does not require pharmacokinetic enhancement (boosting) with a CYP3A inhibitor	Minimal resistance to bictegravir and B/F/TAF was observed. If approved, B/F/TAF will provide an unboosted INSTI-containing FDC treatment option with less drug-drug interactions than E/C/F/TAF.
Risk	• The safety data submitted with this NDA demonstrate a favorable safety profile. The adverse drug reaction (ADR) that occurred in at least two percent of subjects on B/F/TAF was abdominal pain, which is currently labelled based on review of the adult safety data. • Notable Grade 3 or 4 elevations of laboratory abnormalities ≥ 2% occurred for neutrophils (decreased) and amylase; these elevations were not associated with clinical AEs (i.e. increased infections from neutropenia and pancreatitis from increased amylase). • Grade 1 or 2 elevation in bilirubin occurred in 3% of subjects in the pooled naïve trials and less frequently in the virologically suppressed adult population.	Generally, B/F/TAF was safe and well tolerated in this pediatric population. Adverse reactions and laboratory abnormalities were similar to findings in adults.
Risk Management	• Because TAF and TDF are both prodrugs of TFV, the TAF prescribing information will include safety information contained in the current TDF label. A warning regarding new and worsening renal impairment consistent with other TDF and TAF containing products is listed. • Section 5 will also include a warning for lactic acidosis/severe hepatomegaly with steatosis per class labeling with NRTIs. • Boxed Warning and Section 5 will include a warning regarding severe acute exacerbation of hepatitis B in patients who have discontinued B/F/TAF (due to anti-HBV activity of F/TAF).	Safety considerations can be adequately described in the label. No risk management beyond standard pharmacovigilance is warranted based on this review.

2. Background

B/F/TAF, originally approved in February 2018, is an important product for adults receiving antiretroviral treatment for HIV-1 infection. B/F/TAF is recommended as a preferred integrase inhibitor based single tablet regimen (STR) for initiation of ART in naïve adult patients[2]. The recommended dose of the components of B/F/TAF are bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg). This supplemental NDA contains the results of a single ongoing open label trial, GS-US-380-1474 (Trial 1474), a pharmacokinetic, safety, and antiviral activity study of B/F/TAF in adolescents and pediatric patients.

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

PMR #3322-1: 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.

This submission partially fulfills the PMR above. In addition, this application is a partial response to a Written Request for B/F/TAF. Additional data for pediatric patients 2-6 years old must be submitted and evaluated to fulfill the PMR and data in neonates-18 years old are needed to support the Written Request.

3. Product Quality

There were no CMC or Manufacturing related issues in this submission. The tablets administered in this trial are approved for use in adults with HIV-1; and are commercially available.

4. Nonclinical Pharmacology/Toxicology

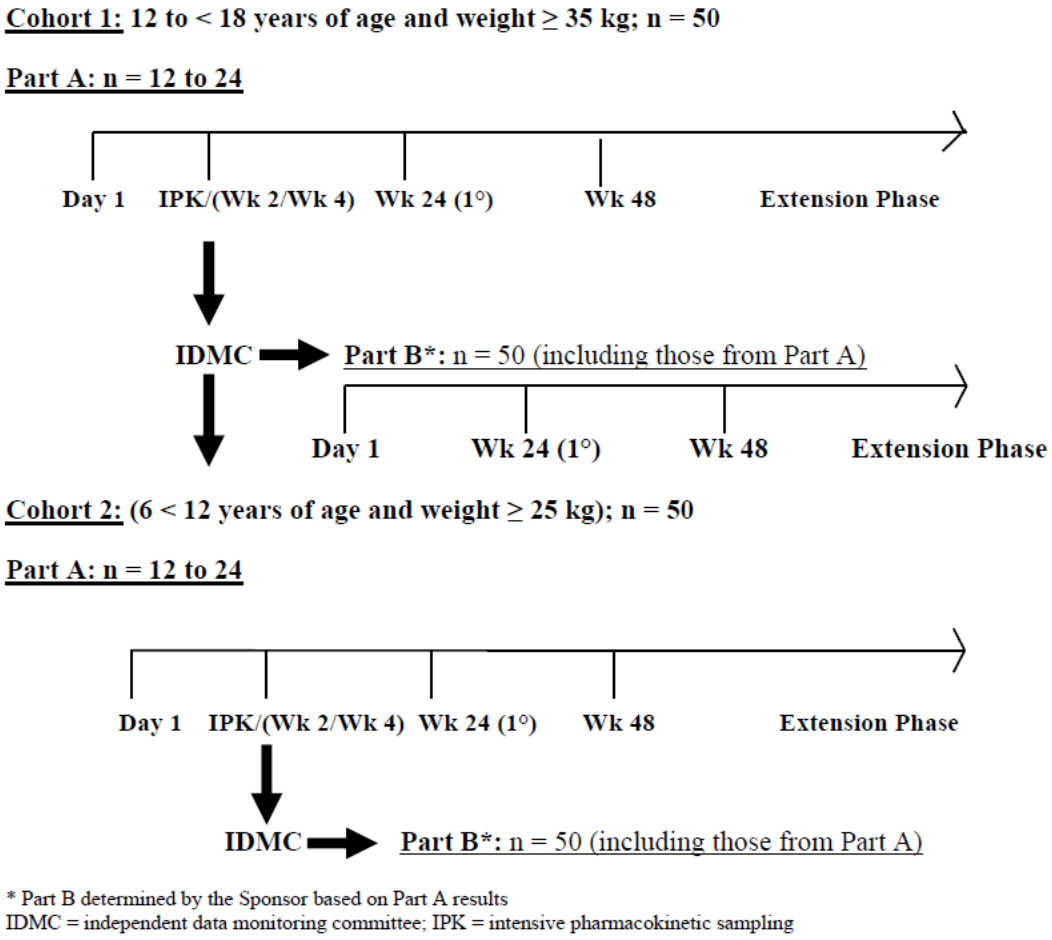
Please see Dr. John Dubinion's review for complete details. Data submitted in this supplement demonstrated that bictegravir was not carcinogenic in a 2-year rat study at doses up to 300 mg/kg/day, which resulted in exposures of approximately 31 times the exposure in humans at the recommended dose of 50 mg BIC in B/F/TAF.

5. Clinical Pharmacology

Trial Design

Safety and efficacy data in HIV-1 infected, virologically suppressed adolescents 12 to 18 years of age weighing ≥ 35 kg (Week 48 for Cohorts 1A and 1B) and children 6 to < 12 years of age, weighing ≥ 25 kg (Week 48 for Cohort 2A and Week 24 for Cohort 2B) were submitted (See Figure 1). Part A of both cohorts were included in the intensive PK assessments. Once the data from Part A were analyzed and dosing confirmed, Part B of the Cohorts were opened for enrollment.

Figure 1: Study Schema Trial 1474



* Part B determined by the Sponsor based on Part A results
IDMC = independent data monitoring committee; IPK = intensive pharmacokinetic sampling

Source: Interim 1 Clinical Study Report, page 29

Key enrollment criteria for eligible subjects were as follows:

- HIV-1 infected adolescents (12 to < 18 years of age, weight ≥ 35 kg) and children (6 to < 12 years of age, weight ≥ 25 kg);
- virologically suppressed (HIV-1 RNA < 50 copies/mL or undetectable HIV-1 RNA if the limit of detection of the local assay used was ≥ 50 copies/mL) for ≥ 6 months prior to screening;
- on a stable antiretroviral regimen comprised of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent;
- estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m2 (as calculated using the Schwartz formula; eGFR Schwartz) at screening;
- and no documented or suspected resistance to FTC, tenofovir (TFV), or integrase strand transfer inhibitors (INSTIs) including, but not limited to, the reverse transcriptase (RT) resistance mutations K65R and M184V/I.

Please see Dr. Hazem Hasan's Clinical Pharmacology review of this application for additional information regarding the pediatric PK results summarized below.

The 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in patients aged 12 to less than 18 years and weighing at least 35 kg relative to adults were outside the pre-defined no effect boundaries (70-143%) (Table 1). The observed 35% decrease in BIC C_{tau}, 27% increase in FTC C_{max}, and 30 % decrease in FTC C_{tau} are not considered clinically significant based on exposure-response relationships.

Table 1: Geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in adolescents relative to adults[a]

PK Parameter	Adolescents Geometric mean (% CV)	Adults[a] Geometric mean (% CV)	% GLSM (90% CI) Adolescents/Adults
BIC C_{tau}	1784.3 (44.4)	2609.9 (35.2)	65.38 (58.32, 73.28)
FTC C_{max} (ng/mL)	2689.2 (34.0)	2127.0 (34.7)	127.15 (111.45, 145.06)
FTC C_{tau} (ng/mL)	64.4 (25.0)	96.0 (37.4)	69.25 (61.55, 77.92)

Source: Summary of Clinical Pharmacology, Tables 2 and 7; verified by Dr. Hazem Hasan
a. Historic data; Trials GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878

The 90% confidence interval (CI) of the geometric least squares mean (GLSM) ratios of some PK parameters of BIC, FTC, and TAF in patients aged 6 to less than 12 years and weighing at least 25 kg relative to adults were outside the pre-defined no effect boundaries (70-143%). The observed 52% increase in BIC C_{max}, 42% increase in FTC AUC_{tau}, 84% increase in FTC C_{max}, 85% increase in TAF AUC_{tau}, 76% increase in TAF C_{max}, and 53% increase in TAF C_{tau} are not considered clinically significant based on exposure-response relationships.

Table 2: Geometric least squares mean (GLSM) ratios of some PK parameters of B, F and TAF in children relative to adults

PK Parameter	Children Geometric mean (% CV)	Adults[a] Geometric mean (% CV)	% GLSM (90% CI) Children/Adults
BIC C_{max} (ng/mL)	9462.8 (24.3)	6145.8 (22.9)	152.70 (142.82, 163.25)
FTC AUC_{tau} (h·ng/mL)	17565.1 (36.9)	12293.6 (29.2)	142.27 (127.33, 158.96)
FTC C_{max} (ng/mL)	3888.4 (31.0)	2127.0 (34.7)	184.72 (162.45, 210.05)

TAF AUC_{tau} (h·ng/mL)	277.5 (40.3)	142.0 (17.3)	182.83 (165.20, 202.34)
TAF C_{max} (ng/mL)	204.8 (44.6)	121.3 (15.4)	153.35 (135.64,173.39)

Source: Summary of Clinical Pharmacology, Tables 3,5, and 8; verified by Dr. Hazem Hasan
a. Historic data; Trials GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, GS-US-380-1878

Coadministration of Biktarvy (BVY) with polyvalent cation (PVC)-containing antacids/supplements

Applicant's proposed changes:

- (b) (4)
-

Clinical Pharmacology did not agree with the Applicant's original proposal. (b) (4) No clinical data to Clinical Pharmacology reviewers' knowledge is available to support the Applicant's assertion that a (b) (4) Analysis of BIC interaction with Calcium and Iron were evaluated by Clinical Pharmacology in the original NDA.

The agreed upon changes follow:

Antacids containing Al/Mg:
BIKTARVY can be taken at least 2 hours before or 6 hours after taking antacids containing Al/Mg. Routine administration of BIKTARVY together with, or 2 hours after, antacids containing Al/Mg is not recommended.

Supplements or antacids containing Calcium or Iron:
BIKTARVY and supplements or antacids containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions together with, or 2 hours after, supplements or antacids containing calcium or iron is not recommended.

6. Clinical Microbiology

With no significant resistance information generated from Trial 1474, the applicant proposed no revisions to be made to the Microbiology section of the label (Section 12.4).

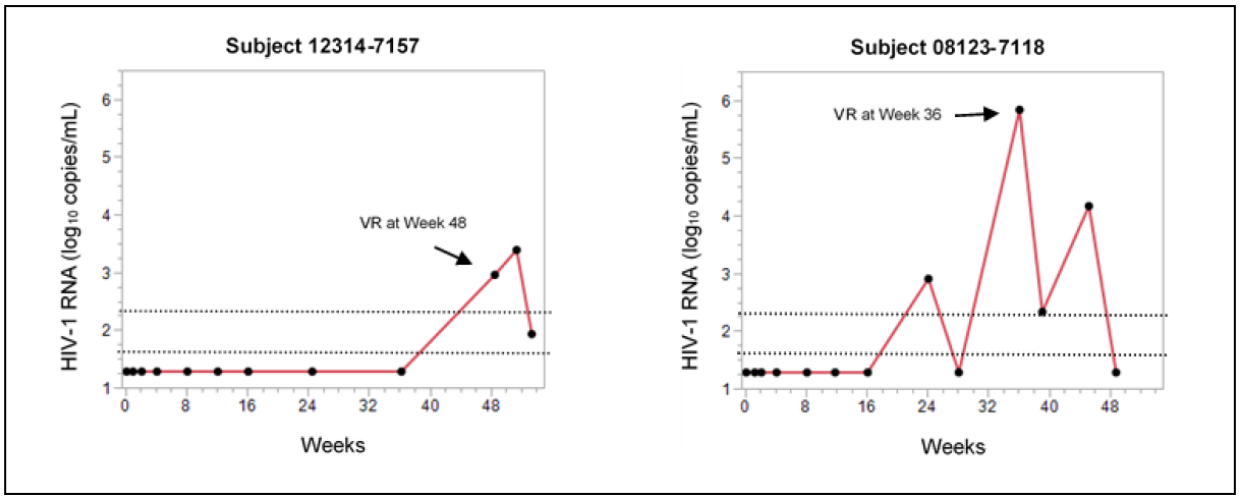
Please see the clinical virology review by Dr. Sung Rhee for the original NDA and Supplement 5. Brief details from her reviews are below.

The resistance analysis population (RAP) was comprised of subjects who experienced confirmed virologic rebound with HIV-1 RNA ≥200 copies/mL.

In the Week-48 analysis, two subjects were included in the RAP (see Figure 2 below):

- Subject [redacted] (b) (6) (Cohort 1; prior ARVs 3TC, ABC, D4T, LPV, RTV): virologic rebound at Week 48
- Subject [redacted] (b) (6) (Cohort 1; prior ARVs 3TC, AZT, LPV, RTV): confirmed but transient virologic rebound at Week 36 and Week 48 (1/2); HIV-1 RNA <50 copies/mL at Week 48 (2/2)

Figure 2. HIV-1 Viral Load in Subjects Who Experienced Confirmed Virologic Rebound



Source: Dr. Sung Rhee's analysis, based on ADEFF dataset; VR=virologic rebound

Further, post-baseline genotypic data from the two resistance-testing eligible subjects showed no detection of primary substitutions associated with B/F/TAF resistance. The samples that provided this information were from HIV-1integrase/HIV-1 reverse transcriptase (IN/RT) data from Subject [redacted] (b) (6) Week-36 sample (213 copies/mL) and the IN data from Subject [redacted] (b) (6) Week-48 sample (904 copies/mL).

7. Clinical Efficacy

As stated previously, the sNDA partially fulfills the outstanding PREA PMR for B/F/TAF which required pharmacokinetic, safety, and antiviral activity data in pediatric patients from 2 to less than 18 years of age. The clinical trial report focused on the 48-week safety and efficacy analyses for Cohort 1 (virologically-suppressed adolescents 12 to less than 18 years; at least 35 kg) and 24-week safety and efficacy analysis for Cohort 2 (virologically-suppressed children (6 to less than 12 years; at least 25 kg). Therefore, the efficacy section of this review summarizes the Week 48 efficacy results for Trial 1474 Cohort 1 and Week 24 efficacy results from Cohort 2. Data collection from both Cohorts is ongoing.

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

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

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two parameters, HIV RNA viral load and CD4 count. Antiretroviral drugs including NRTIs, NNRTIs, PIs, and INSTIs are shown to lower HIV RNA, improve CD4 counts (or percentages) and improve general clinical outcome in adult and pediatric subjects. Treatment recommendations are very similar across all age groups.[2]

Trial 1474 was reviewed for efficacy, safety and tolerability, and pharmacokinetics. Subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results were reviewed using JMP Statistical software and JReview.

Demographics and Baseline Characteristics

A total of 102 subjects were screened for study participation, and 100 subjects received at least one dose of study drug (B/F/TAF) and are included in the Full Analysis Set. There were 50 subjects each in Cohort 1 and 2. There were no premature discontinuations.

The demographic and baseline characteristics of the trial subjects are described below and summarized in Table 3.

Cohort 1

The majority of subjects were female (64%) and Black/African American (65%). The mean age of the subjects was 14 years. The mean weight was 51.7 kg with a weight range of 40.0 to 56.1 kg. The median weight was 44.7 kg with a first quartile of 27.5 kg and a third quartile of 33.0; therefore, an acceptable range of weights was studied.

As specified in the study protocol, all 50 subjects had baseline HIV RNA <50 copies/mL. At baseline, median CD4+ cell count was 750 cells per mm^3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%). The majority of subjects (N=45, 90%) acquired HIV via mother-to-child transmission, and the mean number of years since diagnosis was 11.6. The HIV disease status for 92% subjects was asymptomatic.

Cohort 2

The majority of subjects were female (54%) and Black/African American (72%). The mean age of subjects was 10 years. The mean weight was 31.9 kg with a weight range of 25.0 to 69.1 kg. The median weight was 29.0 kg with a first quartile of 29.6 kg and a third quartile of 32.5; therefore, an acceptable range of weights was studied.

As specified in the study protocol, all 50 subjects had baseline HIV RNA <50 copies/mL. At baseline, median CD4+ cell count was 898 cells per mm^3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%). The majority of subjects (N=48, 96%) acquired HIV via mother-to-child transmission, and the mean number of years since diagnosis was 8.9. The HIV disease status for 94% subjects was asymptomatic.

Table 3: Demographic Characteristics

Subgroup	Cohort 1: 12 to <18 Years (N = 50) n (%)	Cohort 2: 6 to <12 years (N = 50) n (%)	Total (N = 100) n (%)
Sex			
Female	32 (64)	27 (54.0)	59 (59.0)
Male	18 (36)	23 (46.0)	41 (41.0)
Age (years)			
Mean	14.44	9.64	12.04
Standard Deviation	1.76	1.47	2.9
Minimum	12	6	6
Median	15	10	11.5
Maximum	17	11	17
Race			
Asian	13 (26.0)	11 (22.0)	24 (24.0)
Black or African American	32 (64.0)	36 (72.0)	68 (68.0)
Native Hawaiian or Other Pacific Islander	1 (2.0)	0 (0.0)	1 (1.0)
Other	3 (6.0)	1 (2.0)	4 (4.0)
White	1 (2.0)	2 (4.0)	3 (3.0)
Ethnicity			
Hispanic or Latino	2 (4.0)	0 (0.0)	2 (2.0)
Not Hispanic or Latino	48 (96.0)	50 (100.0)	98 (98.0)
Region			

Subgroup	Cohort 1: 12 to <18 Years (N = 50) n (%)	Cohort 2: 6 to <12 years (N = 50) n (%)	Total (N = 100) n (%)
Africa	26 (52.0)	28 (56.0)	54 (54.0)
Asia	12 (24.0)	10 (20.0)	22 (22.0)
United States	12 (24.0)	12 (24.0)	24 (24.0)
BASELINE WEIGHT (kg)			
Mean	51.71	31.86	41.78
Standard Deviation	18.38	8.02	17.28
Minimum	35.4	25	25
Median	44.65	29	38.85
Maximum	122.8	69.1	122.8
BASELINE BMI (kg/m^2)			
Mean	21.37	17.26	19.31
Standard Deviation	6.45	2.43	5.27
Minimum	16.22	13.93	13.93
Median	19.12	16.69	18.04
Maximum	45.66	27.23	45.66
BASELINE HEIGHT (cm)			
Mean	154.74	135.08	144.91
Standard Deviation	7.85	8.07	12.66
Minimum	137.2	122	122
Median	155.5	133.3	145.75
Maximum	173.1	159.3	173.1
CD4+ CELLS BASELINE (cells/µL)			
Mean	750.86	930.38	840.62
Standard Deviation	224.39	309.87	283.88
Minimum	337	390	337
Median	749.5	898	809.5
Maximum	1207	1991	1991
HIV STATUS			
AIDS	0 (0.0)	1 (2.0)	1 (1.0)
Asymptomatic	46 (92.0)	47 (94.0)	93 (93.0)

Subgroup	Cohort 1: 12 to <18 Years (N = 50) n (%)	Cohort 2: 6 to <12 years (N = 50) n (%)	Total (N = 100) n (%)
Symptomatic HIV Infection	4 (8.0)	2 (4.0)	6 (6.0)
HIV YEARS INFECTED			
Mean	11.58	8.88	10.23
Standard Deviation	3.63	2.14	3.26
Minimum	3	2	2
Median	12	10	10.5
Maximum	17	11	17
PERCENT CD4+ CELLS BASELINE (%)			
Mean	33.61	35.85	34.73
Standard Deviation	6.23	6.97	6.67
Minimum	18.8	19.2	18.8
Median	32.9	36.5	34.75
Maximum	45.2	52.5	52.5

Source: FDA Demographic Tool using the ADSL and ADAE dataset.

Subjects were switched from a stable ARV regimen to B/F/TAF. The antiretroviral medications received prior to the first dose of B/F/TAF are shown in the following table (Table 4).

Table 4: Antiretroviral Medications Prior to Switch to B/F/TAF

Analysis Medication Class	Standardized Medication Name	Cohort 1	Cohort 2
INSTI	DOLUTEGRAVIR	1 (1%)	0
	ELVITEGRAVIR	4 (4%)	0
	RALTEGRAVIR	0	4 (4%)
NNRTI	EFAVIRENZ	12 (12%)	13 (13%)
	ETRAVIRINE	1 (1%)	1 (1%)
	NEVIRAPINE	13 (13%)	14 (14%)
	RILPIVIRINE	1 (1%)	1 (1%)
NRTI	ABACAVIR	13 (13%)	17 (17%)
	COMBIVIR	5 (5%)	14 (14%)
	DIDANOSINE	5 (5%)	1 (1%)
	EMTRICITABINE	5 (5%)	1 (1%)
	EPZICOM	6 (6%)	9 (9%)
	LAMIVUDINE	39 (39%)	44 (44%)
	STAVUDINE	11 (11%)	10 (10%)
	TENOFOVIR AF	1 (1%)	0
	TENOFOVIR DF	8 (8%)	0
	TRUVADA	2 (2%)	1 (1%)

	ZIDOVUDINE	25 (25%)	34 (34%)
PI	ATAZANAVIR	6 (6%)	5 (5%)
	DARUNAVIR	1 (1%)	3 (3%)
	INDINAVIR	1 (1%)	0
	KALETRA	17 (17%)	28 (28%)
	NELFINAVIR	1 (1%)	1 (1%)
	RITONAVIR	8 (8%)	11 (11%)

Source: ADCM dataset

INSTIs in general have better tolerability than PIs. It is notable that under 5% of subjects in either cohort were on INSTI based regimens prior to the switch. Zidovudine, an NRTI, can cause neutropenia and can have issues with tolerability. It is notable that 25%-34% of subjects were on zidovudine as part of their regimen.

HIV Plasma Viral Load Analysis

The proportion of subjects with plasma viral load < 50 copies/mL at Week 48 (based on FDA snapshot algorithm) for Cohort 1 was 98% (49/50), and the proportion of subjects with plasma viral load < 50 copies/mL at Week 24 for Cohort 2 was 100% (50/50). One subject (Subject (b) (6)) in Cohort 1 had detectable HIV-1 viral load of 940 copies/mL at Week 48 (Day 340) that was confirmed with an HIV-1 viral load of 2,430 copies/mL at Day 360; however, no detection of primary substitutions associated with B/F/TAF resistance were found. From an efficacy standpoint, it was clear that the majority of subjects were able to remain virologically suppressed through 48 and 24-weeks, respectively (Table 5).

Table 5: Summary of Efficacy Data from Trial 1474

Design	**Number dosed**	**Primary endpoint**	**Findings: Plasma HIV-1 RNA<50 c/mL n/N (%) 95% CI***	
Phase 2/3, OL, MC, multicohort, SA study with treatment duration ≥ 48 weeks	Cohort 1: n = 50 Cohort 2: n = 50	Proportions of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48	Week 24	Week 48
			Cohort 1: 50/50(100.0%) (92.9%, 100.0%) Cohort 2: 50/50(100.0%) (92.9%, 100.0%) Cohort 1 +Cohort 2: 100/100 (100.0%) (96.4%, 100.0%)	Cohort 1: 49/50 (98.0%) (89.4%,99.9%) Cohort 2: 25/25 (100.0%) (86.3%, 100.0%) Cohort 1+Cohort 2: 74/75 (98.7%) (92.8%, 100.0%)

OL=Open-level, MC= Multicenter; SA= Single Arm; * =Clopper-Pearson exact

Source: Information from Table 16 of Clinical Study Report verified by Mushfiqur Rashid, PhD, Office of Biometrics

CD4+ Cell Analysis

CD4+ cell declines were observed in virologically-suppressed children aged 6-12 who switched ART regimens to elvitegravir (E), cobicistat (C), emtricitabine (F), tenofovir alafenamide (TAF) (E/C/F/TAF, GENVOYA®), another INSTI based FDC.[4] The CD4 declines were observed in virologically suppressed 6-12-year olds who were administered E/C/F/TAF in Trial GS-US-292-0106 and are summarized in Table 6 below. Of note, the CD4 decline was a rapid mean decrease of approximately 160 cells/uL at Week 2, which remained consistently decreased through Week 24. It has been theorized that the INSTI, elvitegravir may have caused inhibition of RAG1/2 function leading to the declines; however, further evaluation and review of this theory is ongoing. Gilead asserts that the CD4 cell count declines in Trial 0106 are likely due to fluctuations in lymphocyte counts in response to various intrinsic and extrinsic stimuli, the impact of aging on lymphocyte subset numbers, and the regression to the mean in subjects with a high CD4+ counts at baseline. Additionally, the applicant has performed analysis of T, B and NK lymphocyte subset changes between the similar aged cohorts in Trial 0106, the B/F/TAF cohort 2 in Trial 1474 and an external observational cohort (Pediatric HIV/AIDS Cohort Study; PHACS) of virologically suppressed children. This analysis did not support that the impairment of RAG is responsible for the decline of CD4+ cell count.

Table 6: CD4+ Count Decline Analysis: Mean and % Change in CD4+ Count from Baseline (BL) to Week (Wk) 24 for Virologically Suppressed 6-12-year-olds on E/C/F/TAF in Trial GS-US-292-0106.

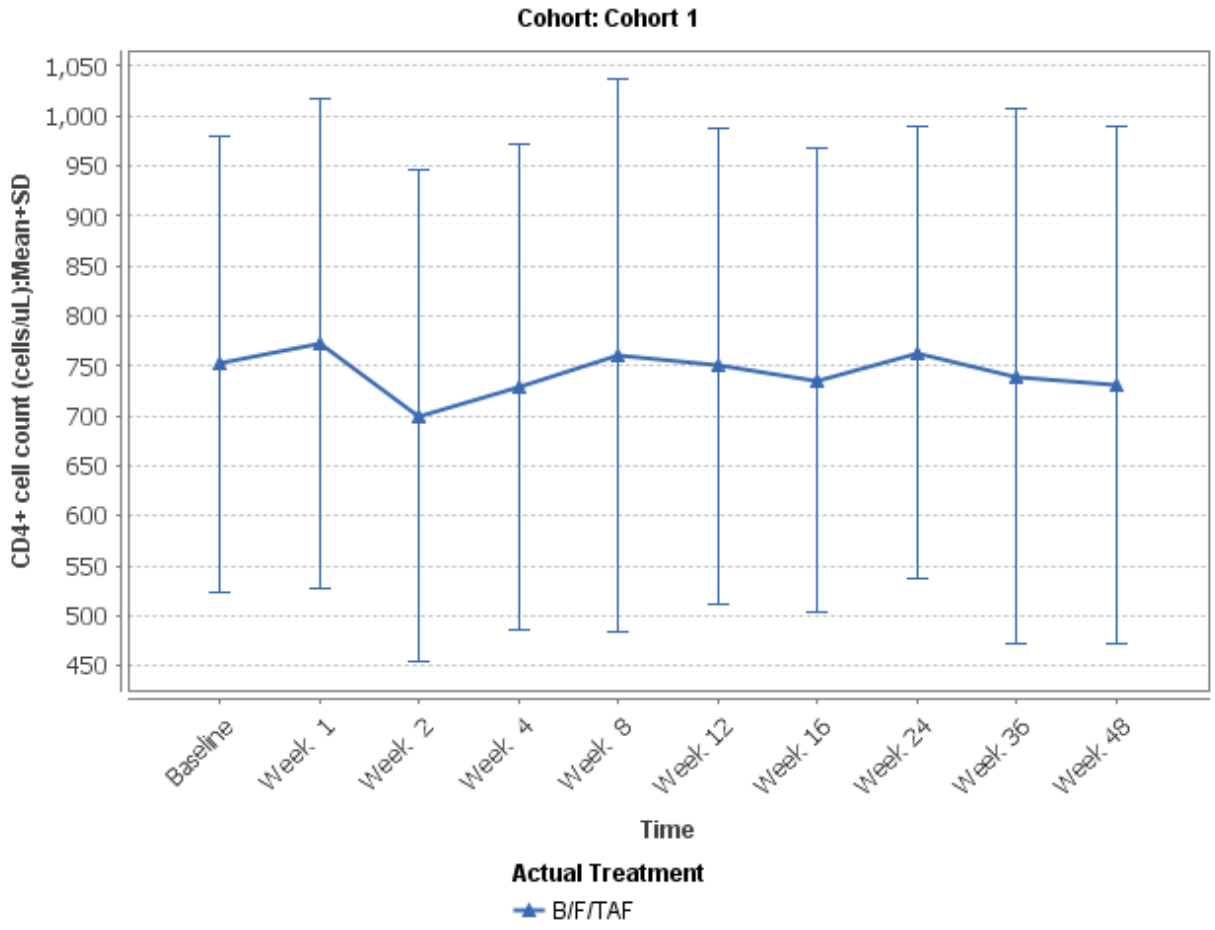
		Mean Change from BL					
	BL	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24
CD4+count (cells/uL)	966 (201) *	-162	-125	-134	-162	-133	-150
CD4%	40 (5.3) *	-0.5%	-0.1%	-0.8%	-0.8%	-0.5%	-1.5%

*Mean (SD)
Source: Bell T, et al. Poster presentation at IDSA[4] and parts of this information are also in USPI for GENVOYA®

Because of the observed CD4+ declines in a similar age cohort of virologically suppressed 6-12-year olds on E/C/F/TAF, CD4+ count trends were evaluated for both age cohorts in Trial 1474. The mean CD4+ cell counts demonstrated small declines of approximately 20-27 cells/uL by Week 48 as summarized in Figure 3 for Cohort 1 and Figure 4 and Table 7 for Cohort 2. In Trial 1474 per the Applicant, subjects in Cohort 1 started with a mean (SD) CD4+ cell count of 751 (224.4) cells/uL[3]. After switching to B/F/TAF, the mean change from baseline in CD4+ cell count for Cohort 1 at Week 48 was -22 cells/uL, and the mean CD4% (SD%) change at Week 48 was 0.5% (3.41%). Per the Applicant, subjects in Cohort 2 started with a mean (SD) CD4+ cell count of 930 (309.9) cells/uL. After switching to B/F/TAF, the mean change from baseline in CD4+ cell count for Cohort 2 at Week 24 was -24 cells/uL, and the mean CD4% (SD%) change at Week 24 was 0.8% (3.55%). In our analysis for Cohort 2, subjects had a baseline mean (SD) CD4+ cell count of 929 (309) cells/uL. After switching to B/F/TAF, the mean change from baseline in CD4+ cell count for Cohort 2 at Week 24 was -27 cells/uL. The reviewers' analyses (by Dr. Wendy Carter and Dr. Tanvir Bell), showed small differences from the Applicant's analyses, explained by the specific values chosen for the analyses from multiple lab results per individual subject within the treatment window.

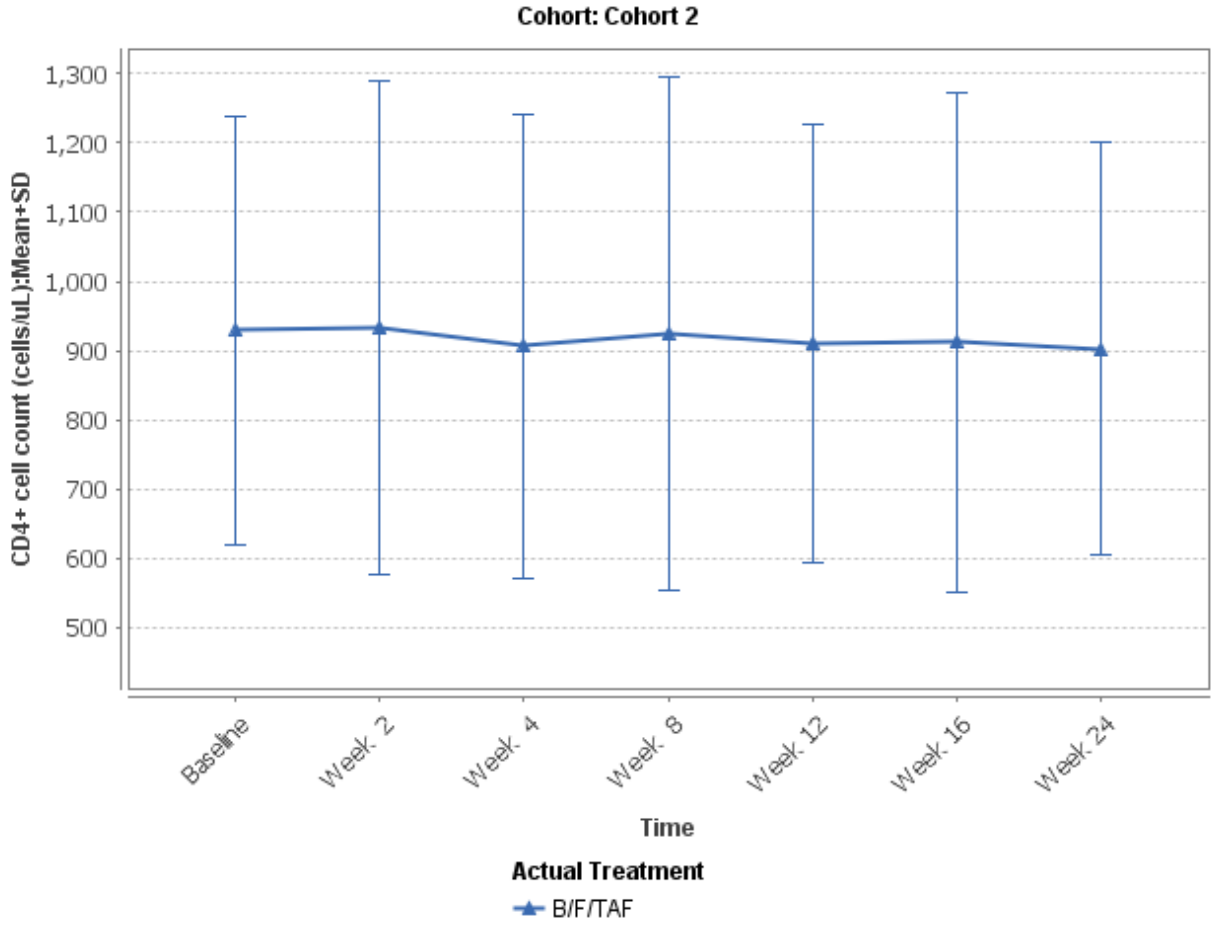
Marked declines in CD4+ count were not observed in pediatric patients aged 6 to 12 switched to B/F/TAF as were seen in subjects switched to E/C/F/TAF in a similar age group, as described above (see Appendix 2 for additional figures) Overall, the small declines observed in CD4+ cells observed in both cohorts in Trial 1474 were not clinically significant and likely consistent with frequent sampling and normal lymphocyte variation. Additionally, the CD4% remained stable through Week 48 for Cohort 1 (data not shown) and Week 24 for Cohort 2 (Table 7).

Figure 3: Mean (SD) CD4+ Cell Count Changes in Cohort 1 Over 48 Weeks



Source: ADLB and ADSL datasets

Figure 4: Mean (SD) CD4+ Cell Count Changes in Cohort 2 Over 24 Weeks



Source: ADLB and ADSL datasets

Table 7. CD4+ Count Decline Analysis: Mean Change from Baseline in CD4+ Count to Week 24 for Virologically Suppressed 6-12-year-olds on B/F/TAF

	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
CD4+ cell count mean	929	933	906	924	911	912	902
SD	309	256	336	370	316	360	398
CD4% Mean	36	37	37	35.5	36.1	36.2	37
SD	6.9	6.8	7.1	7.1	6.4	6.1	6.9

Unit for CD4+ is (cells/uL); SD=Standard Deviation
Source: ADEFF and ADLB datasets

8. Safety

The data submitted in this Supplement support the safety and tolerability of B/F/TAF. The Applicant has submitted safety data on 100 pediatric patients with at least 24-week safety data. B/F/TAF was generally safe and tolerated in pediatric subjects weighing at least 25 kg. No new safety issues were identified. The adverse events (AEs) reported were similar to those reported

in adults. The study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings. In the following safety sections, AE MedDRA preferred terms are in italics.

Deaths and SAEs

There were no deaths up to Week 48. There were two SAEs that follow:

- Subject (b) (6) is a 16-year-old (yo) female who was hospitalized due to Grade (G) 2 *abdominal pain* on D124-132. The cause of the abdominal pain is unclear and unrelated to study drug. Study drug was continued.
- Subject (b) (6) is a 16 yo female with history of pulmonary tuberculosis who was hospitalized due to G2 *lung abscess* on D299-308 and was treated with IV fluids and antibiotics. Study drug was continued.

The Sponsor submitted a 90-day safety update on March 19, 2019 and reported an SAE from a subject (Subject (b) (6)) with hyperthyroidism with diarrhea not related to study drug and study drug was continued.

For the three SAEs above, study drug was continued, and no new safety signals were identified.

Discontinuations due to Adverse Events

One subject discontinued due to AEs. Subject (b) (6) is 7 yo female with h/o ADHD who experienced drug related G2 *anxiety* on D137 (data analysis showed no end date) and drug related G2 *insomnia* (data analysis showed no start date) end date of D141, the day the study drug was discontinued. The AEs that led to discontinuation occurred temporally later in the course of treatment making immediate drug related untoward effects less likely.

The 90-day safety update reported a 17 yo female (Subject (b) (6)) that became pregnant and discontinued study drug on (b) (6) (Day 592 of trial). The subject's pregnancy was uncomplicated through this safety update data-cut date ((b) (6)). Her estimated due date is (b) (6) Because dolutegravir, another integrase inhibitor, has been associated with neural tube defects in the Tsepamo study from Botswana, the review team will be interested in following the infant outcome from this patient in the future.

Treatment Emergent Adverse Events and Adverse Drug Reactions

A total of 69 (69%) subjects had Treatment-Emergent AEs (TEAEs). Of those, 10 (10%) were assessed as related to the study drug by the investigator (i.e. ADRs) (see Table 8). Only abdominal discomfort was reported by 2 subjects; all other treatment-emergent ADRs were reported by a single subject.

Table 8: Treatment-Emergent ADRs by Body System Organ Class and Preferred Term

Body System or Organ Class	Preferred Term	B/F/TAF N=100
Gastrointestinal disorders	Abdominal discomfort	2 (2%)
	Diarrhea	1 (1%)
	Vomiting	1 (1%)
General disorders and administration site conditions	Fatigue	1 (1%)
Investigations	Amylase increased	1 (1%)
Metabolism and nutrition disorders	Decreased appetite	1 (1%)
	Increased appetite	1 (1%)
Nervous system disorders	Dizziness	1 (1%)
	Headache	1 (1%)
Psychiatric disorders	Anxiety	1 (1%)
	Insomnia	1 (1%)
Skin and subcutaneous tissue disorders	Rash	1 (1%)
Total		10 (10%)

Source: ADAE dataset

All the above ADRs were reported as Grade 1 or 2. The USPI in Section 6 describes the ADRs from the B/F/TAF adult Trials 1489 and 1490 and includes abdominal pain, the only Preferred Term (PT) in this trial that occurred at ≥ 2% in this trial. Additionally, the majority of the other PTs in Table 7 are described in Section 6 of the current label.

Laboratory Abnormalities

Laboratory abnormalities were reported in 94 (94%) subjects through Week 24. The majority of laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 or Grade 4 laboratory abnormalities were reported in 18 (18%) subjects; and Grade 4 laboratory abnormalities were reported in 2 (2%) of subjects. The percentages of subjects reporting Grade 3 abnormalities were 11% with urine erythrocytes, 6% with occult blood, 3% with neutrophils (decreased), 3% with amylase, and 1% with bicarbonate. One subject (1%) each reported a Grade 4 abnormality of segmented neutrophils (decreased) and potassium (hyperkalemia). Laboratory abnormalities occurring in ≥ 2% of subjects are further characterized below.

The most frequently reported Grade 3 abnormality was urine Red Blood Cells (hematuria, quantitative, or dipstick) in 11 (11%) subjects. The majority of Grade 3 elevations were isolated abnormalities. Two subjects (2%) had associated reported UTIs. One subject (Subject (b) (6)) reported the MedDRA preferred term of Grade 1 *crystal urine present* (verbatim reported term: *intermittent urine calcium oxalate crystals*) on Day 176 onwards, and Grade 2 *hematuria* Day 56 onwards. Further analyses showed that the clear majority of the Grade 3 urine Red Blood Cells abnormalities were among girls and may be attributed to menstruation. All AEs with Grade 3 elevation of urine Red Blood Cells were assessed by the investigator as not related to the study drug and did not lead to drug discontinuation. There is no clear pattern of drug associated hematuria amongst these subjects and the alternative explanations provided above could account for the reported laboratory abnormalities.

The 6% of subjects who reported fecal occult blood may also be attributed to contamination of the testing due to menstruation because all abnormalities were in females. Further review of subject level data found no pattern of drug-related AEs to suggest a pattern of concern with the events of fecal occult blood.

Neutrophils (decreased) accounted for 3 (3%) of subjects with Grade 3 abnormalities and one subject with a Grade 4 abnormality. Of the subjects with Grade 3 decrease neutrophils, one subject had a transient decrease, and two subjects had decreases at baseline and throughout the treatment course. The subject with Grade 4 decreased neutrophils was reported at enrollment while the child was on an AZT based regimen, and it improved shortly after starting B/F/TAF. AZT is associated with neutropenia and it is likely to be related to the Grade 4 neutropenia in this case, particularly since the neutropenia improved on B/F/TAF. In conclusion, none of these neutrophils (decreased) appear to be study drug related.

Three subjects reported (3%) Grade 3 amylase elevations; one subject with isolated and transient elevations while the other two subjects had sustained amylase elevations, but no GI associated AEs or pancreatitis associated with the elevations. The one subject with sustained amylase elevation and concomitant lipase elevation is described as follows (the other two did not have lipase elevation).

- Subject (b) (6) 15 yo AA male with Grade 1 *amylase increase* (AE dataset), which was Grade 3 amylase elevation in the LB database, D422-435. This event was shortly after a reported tooth abscess on d401-407, which may explain an elevated amylase from an oral source. The subject had lipase values that were for the most part within normal limits. A Grade 1 lipase elevation of 128 U/L (normal 0-63 U/L) was reported on D 422, however another lipase on that same day was normal at 27 U/L. No GI AEs or pancreatitis were reported.

The rate of amylase elevations observed in the adult treatment-naïve trials that are currently included in the label are similar to the 2% rate of Grade 3-4 elevations in amylase observed in Trial 1474.

Submission Specific Safety Analysis

The clinical review of the initial NDA 210251 application included the submission-specific safety issues of hepatic safety, psychiatric AEs of interest, rash and hypersensitivity reactions, renal analysis, and bone analysis because of drug (i.e. TAF versus TDF), drug class (i.e. INSTI), or HIV disease specific safety concerns. The hepatic safety analysis is discussed in more detail first, and the other submission-specific safety issues follow.

Hepatic safety

A hepatobiliary analysis was performed to evaluate the potential for hepatotoxicity from B/F/TAF because the hepatobiliary system (with gastrointestinal intolerance) was identified as

the target organ of toxicity in repeat-dose toxicology studies in mice, rats, and monkeys, and because antiretroviral drugs in general have been associated with hepatotoxicity.

No Hy's law cases were identified in Trial 1474. No Grade 3 or 4 changes in ALT, AST, or bilirubin were identified. Grade 1 ALT elevations occurred in 9% of subjects in Trial 1474. My initial NDA review adult switch trials in virologically suppressed patients revealed about 15%-17% Grade 1 ALT elevations from B/F/TAF compared with 7%-8% in comparator arm (staying on background regimen). This difference in Grade 1 ALT elevations was not labelled because these post baseline elevations were not associated with hepatic AEs, other liver enzyme test abnormalities, or drug discontinuations. A total of 3 subjects (3%) had graded bilirubin elevations occur during Trial 1474: 2 subjects with G1 bilirubin elevations and one subject with G2 bilirubin elevation. The USPI (from adult naïve trial) lists total 12% of subjects with graded bilirubin elevations: 9% of subjects had G1 bilirubin elevations and 3% of subjects had G2 bilirubin elevations. In conclusion, the isolated changes in ALT or AST and in bilirubin observed in this pediatric population were similar to findings in adults exposed to B/F/TAF. There was no clinical evidence of hepatotoxicity observed in these pediatric cohorts.

No subjects in this trial had Hepatitis B or C coinfection.

Other submission specific AEs

The one psychiatric AE of interest of *insomnia* was further detailed in Discontinuations Due to Adverse Events section. Hypersensitivity reactions including life-threatening skin reactions have been identified for raltegravir and dolutegravir, both other integrase inhibitors, but not with B/F/TAF thus far. One subject in Trial 1474 had a skin related event of G1 severity and was transient is described following.

- Subject (b) (6) 11 yo AA F with G1 *rash* on D2-11. Drug continued no additional medication given.

Per protocol, subjects had an estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m2 (as calculated using the Schwartz formula; eGFR Schwartz) at screening because the premise of this pediatric study included a key PK analysis, and renal insufficiency could confound the interpretation of the PK data. Therefore, the safety data did not reveal any clinically significant renal AEs. No cases of Fanconi's syndrome were identified, although a predilection for Fanconi's syndrome may be less with higher GFR levels.

No Dual-energy X-ray absorptiometry (DXA) scans were done in this trial and no fractures or bone related abnormalities were reported.

In summary, no new signals were detected for the submission-specific safety issues of hepatic safety, rash and hypersensitivity reactions, psychiatric AEs of interest, renal, and bone safety.

Pediatric Parameters

Body Weight and Height

Body weight and height Z-scores were calculated based on the Centers for Disease Control and Prevention (CDC) growth chart. Z-scores are established to compare an individual's weight and height in relation to other individuals of the same age, sex, weight, and ethnic or racial origin. The score itself is the number of standard deviations above or below the mean, which is scored as 0. A score of -2 or lower is concerning for a height or weight that is significantly lower than the norm.

Body weight and height Z-scores for the cohorts in Trial 1474 are shown in Table 9 below.

Table 9: Body Weight and Height Z-Scores

	Cohort 1 N=50					Cohort 2 N=50				
		Z-score		Δ BL*			Z-score		Δ BL*	
PARAMETER	**n**	**Mean**	**Std Dev**	**Mean**	**Std Dev**	**n**	**Mean**	**Std Dev**	**Mean**	**Std Dev**
Height-for-Age Z-Score										
VISIT										
Day 1	50	-1.04	0.96	ref	ref	50	-0.59	1.01	ref	ref
Week 24	50	-0.95	0.89	0.08	0.26	49	-0.59	1.03	0.03	0.21
Week 48	50	-1.00	0.88	0.03	0.32	25	-0.59	1.11	0.08	0.32
We ght-for-Age Z-Score										
VISIT										
Day 1	50	-0.51	1.39			50	-0.39	1.12		
Week 24	50	-0.34	1.40	0.17	0.33	49	-0.12	1.11	0.28	0.30
Week 48	50	-0.32	1.44	0.19	0.47	25	-0.12	1.13	0.41	0.45

*Δ BL=change from baseline; ref=reference
Source: ADVS dataset; Note: some values are slightly different form the Applicant's values

In the adolescent cohort (Cohort 1 parts A and B) the weight-for-age Z-score remained stable and were close to -1.0 from baseline to Week 48. In the pediatric cohort (Cohort 2 parts A and B), the weight-for-age Z-score started lower than normal and increased and came closer to normal (Z score=0) at 24 weeks. Therefore, no effect on body weight and height were observed in the adolescent and pediatric cohorts of Trial 1474.

Tanner Staging

For the study population of 12 to 18-year-olds, the majority of males were categorized at Tanner Stage 1-3 (Stage 3 is enlargement of the penis and growth of the testes) at enrollment; while the majority of the females were categorized at Tanner Stage 4-5 (Stage 5 is mature stage).

As expected for the study population of 6 to < 12-year-olds, the majority of males and females in both treatment groups were categorized at Tanner Stage 1 (prepubertal) at enrollment for each category (male genitalia size and lack of pubic hair and female breast size and lack of pubic hair).

Changes in Tanner stages for pubic hair and genitalia in males and pubic hair and breasts in females from baseline to Weeks 24 and 48 were consistent with the pediatric study population aged 6 to < 18 years.

Safety Summary

In summary, no new safety signal or changes in the frequency of previously described AEs were identified for B/F/TAF. Overall, the findings in Trial 1474 are consistent with previously described adverse events and adverse reactions observed with the use of B/F/TAF in HIV-infected adults. There were no deaths, non-fatal serious or severe (grade 3 or higher) treatment-related events reported. There was no significant hepatic- or skin- related events. There was no grade 3 or higher liver-related laboratory abnormalities. One subject discontinued treatment due to insomnia and anxiety related to B/F/TAF but discontinued over 100 days after starting B/F/TAF.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary.

10. Other Relevant Regulatory Issues

None

11. Labeling

The B/F/TAF labeling has been updated to reflect changes in the indication, extending the population to HIV-1 infected pediatric patients weighing at least 25 kg. Sections that involved clinical input are detailed below and notable additions from the clinical review team are highlighted. Labeling negotiations are ongoing.

1 Indications and Usage

BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 25 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen ~~for at least 3 months~~ with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

Reviewer comment: For HIV labels with both treatment naïve and switch indications, the suppression timeframe will be deleted.

2.2 Recommended Dosage

BIKTARVY is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIKTARVY is one tablet taken orally once daily with or without food in adults and pediatric patients weighing at least 25 kg.

6.1 Clinical Trials Experience

Clinical Trials in Pediatric Subjects

The safety of BIKTARVY was evaluated in HIV-1 infected virologically-suppressed subjects between the ages of 12 to less than 18 years and weighing at least 35 kg (N=50) through Week 48 (cohort 1), and in virologically-suppressed subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (N=50) through Week 24 (cohort 2) in an open label clinical trial (Trial 1474) *[see Clinical Studies (14.4)]*. No new adverse reactions or laboratory abnormalities were identified compared to those (b) (4) in adults. Adverse reactions were reported in 10% of pediatric subjects. The majority (85%) of the adverse reactions were Grade 1. The adverse reaction reported (b) (4) subjects (regardless of severity) was abdominal pain. One subject (1%) had Grade 2 adverse reactions of insomnia and anxiety that led to discontinuation of BIKTARVY. The other adverse reactions that occurred in single subjects were similar to those seen in adults.

6.2 Postmarketing Experience

The following events have been identified during post approval use of products containing TAF. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders

Angioedema and urticaria

Reviewer comment: The above is being added to all TAF containing products based on review of postmarketing reports in TAF containing products. Please see the review from Dr. Paula Gish, RPh, DPVII dated 09/12/2018 in DARRTs for details.

8.4 Pediatric Use

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

Use of BIKTARVY in pediatric patients between the ages of 6 to less than 18 years and weighing at least 25 kg is supported by trials in adults and by an open-label trial in virologically-suppressed pediatric subjects aged 12 to less than 18 years and weighing at least 35 kg receiving BIKTARVY through Week 48 (cohort 1 of Trial 1474, N=50) and in virologically-suppressed pediatric subjects aged 6 to less than 12 years and weighing at least 25 kg receiving BIKTARVY through Week 24 (cohort 2 of Trial 1474, N=50). The safety and efficacy of BIKTARVY in these pediatric subjects was similar to that in adults [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].

Safety and effectiveness of BIKTARVY in pediatric patients weighing less than 25 kg have not been established.

14 Clinical Studies

(b) (4)

Cohort 1: Virologically-suppressed adolescents (12 to less than 18 years; at least 35 kg)

Subjects in cohort 1 treated with BIKTARVY once daily had a mean age of 14 years (range: 12 to 17) and a mean baseline weight of 51.7 kg (range: 35 to 123), 64% were female, 27% were Asian and 65% were black. At baseline, median CD4+ cell count was 750 cells per mm3 (range: 337 to 1207), and median CD4+% was 33% (range: 19% to 45%).

After switching to BIKTARVY, 98% (49/50) of subjects in cohort 1 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 48. The mean change from baseline in CD4+ cell count at Week 48 was -22 cells per mm3. (b) (4)

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

Subjects in cohort 2 treated with BIKTARVY once daily had a mean age of 10 years (range: 6 to 11) and a mean baseline weight of 31.9 kg (range: 25 to 69), 54% were female, 22% were Asian and 72% were black. At baseline, median CD4+ cell count was 898 cells per mm3 (range 390 to 1991) and median CD4+% was 37% (range: 19% to 53%).

After switching to BIKTARVY, 100% (50/50) of subjects in cohort 2 remained suppressed (HIV-1 RNA < 50 copies/mL) at Week 24. The mean change from baseline in CD4+ cell count at Week 24 was -24 cells per mm^3. (b) (4).

12. Postmarketing Recommendations

None

13. Recommended Comments to the Applicant

None

14. References

1. Centers for Disease Control and Prevention, HIV/AIDS Statistics Overview, HIV Surveillance Report. Available at: https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed April 2, 2019.
2. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at

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3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed April 2, 2019.
4. Bell T, Baylor M, Rhee S, Tracy L, Sampson M, Younis I, Belew W, Carter W, Viswanathan P. FDA analysis of CD4+ cell count declines observed in HIV-infected children treated with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. (Poster Presentation ID Week 2018, San Francisco, CA, October 2018).

Appendix 1- **Clinical Investigator Financial Disclosure**

Clinical Investigator Financial Disclosure
Review Template

Application Number: 210251

Submission Date(s): December 20, 2018

Applicant: Gilead

Product: Biktarvy®

Reviewer: Tanvir Bell, MD

Date of Review: January 15, 2019

Covered Clinical Study (Name and/or Number): Trial 1474

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 107		
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) N/A all investigators provided disclosure

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.

There are 107 investigators involved in the one pivotal study, and one investigator received payments from the Applicant in excess of $25,000. No other conflict of interest was identified by the sponsor. The total number of investigators with disclosable financial interest is 1% (1/107).

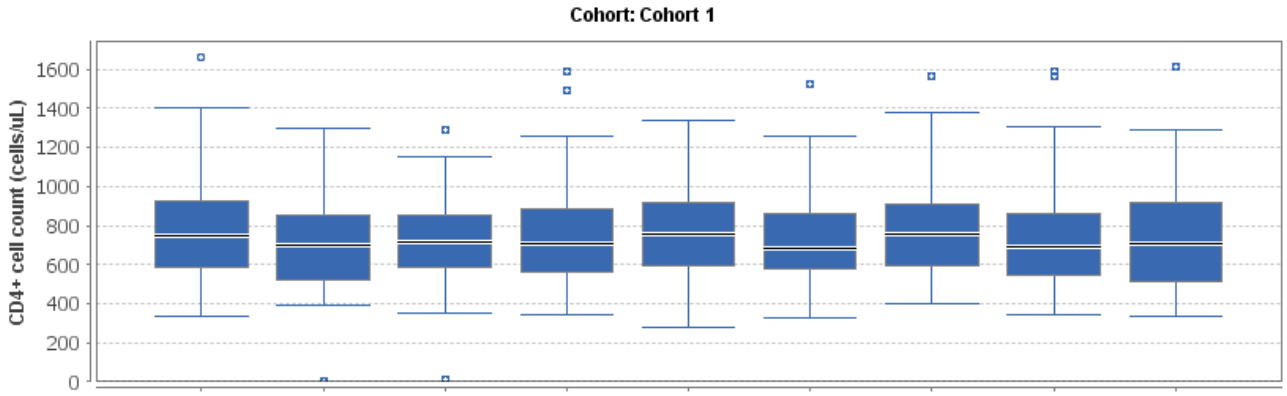
(b) (6) from Site # (b) (6) at (b) (6) accepted significant payments > $25,000. This site enrolled (b) (6) subjects in Trial 1474.

This financial disclosure information is not likely to affect the overall results because Dr. (b) (6) enrolled a (b) (6) %) of the subjects in Trial 1474. The efficacy for the pursued HIV treatment indication relies on objective data, notably PK data and HIV viral load tests that are based on laboratory results and are not subjective investigator-based endpoints, thereby limiting the ability of investigators to influence the efficacy results.

[1] See [web address].

Appendix 2-Additional Graphs of CD4+ Cell Count Trends

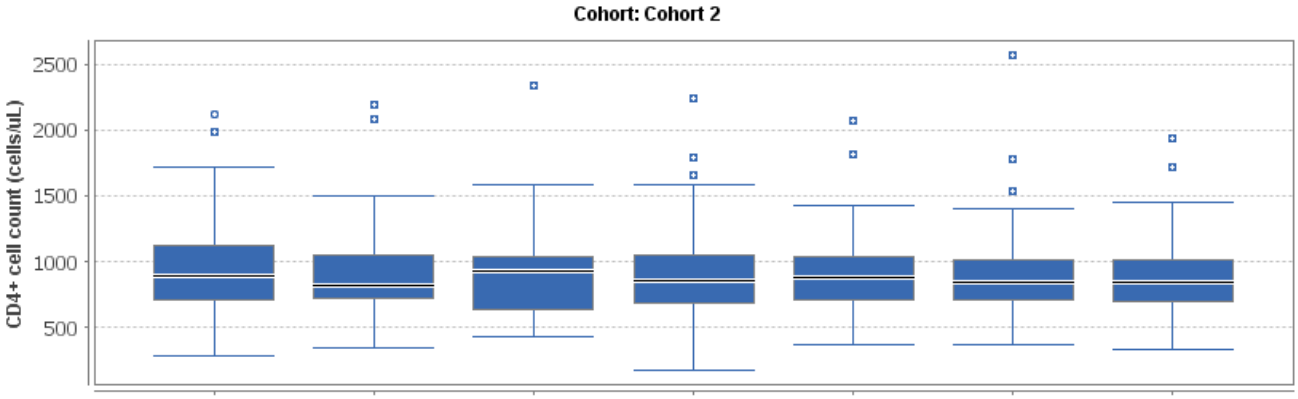
Figure 5. CD4+ Cell Count Trends in Cohort 1



	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 36	Week 48
Mean	752.05	699.92	728.57	760.27	749.96	735.35	763.20	739.44	730.74
Median	745.00	696.00	712.00	708.00	759.00	683.00	757.00	693.00	706.00
Q1	586.00	524.00	589.00	560.00	590.00	580.00	590.00	547.00	516.00
Q3	926.00	854.00	856.00	889.00	919.00	863.00	911.00	858.00	919.00
Min	337.00	2.00	9.00	343.00	277.00	330.00	396.00	345.00	335.00
Max	1663.00	1300.00	1290.00	1586.00	1341.00	1521.00	1563.00	1589.00	1614.00
N	50	49	49	49	50	50	49	50	50

Source: ADEFF and ADLB datasets

Figure 6. CD4+ Cell Count Trends in Cohort 2

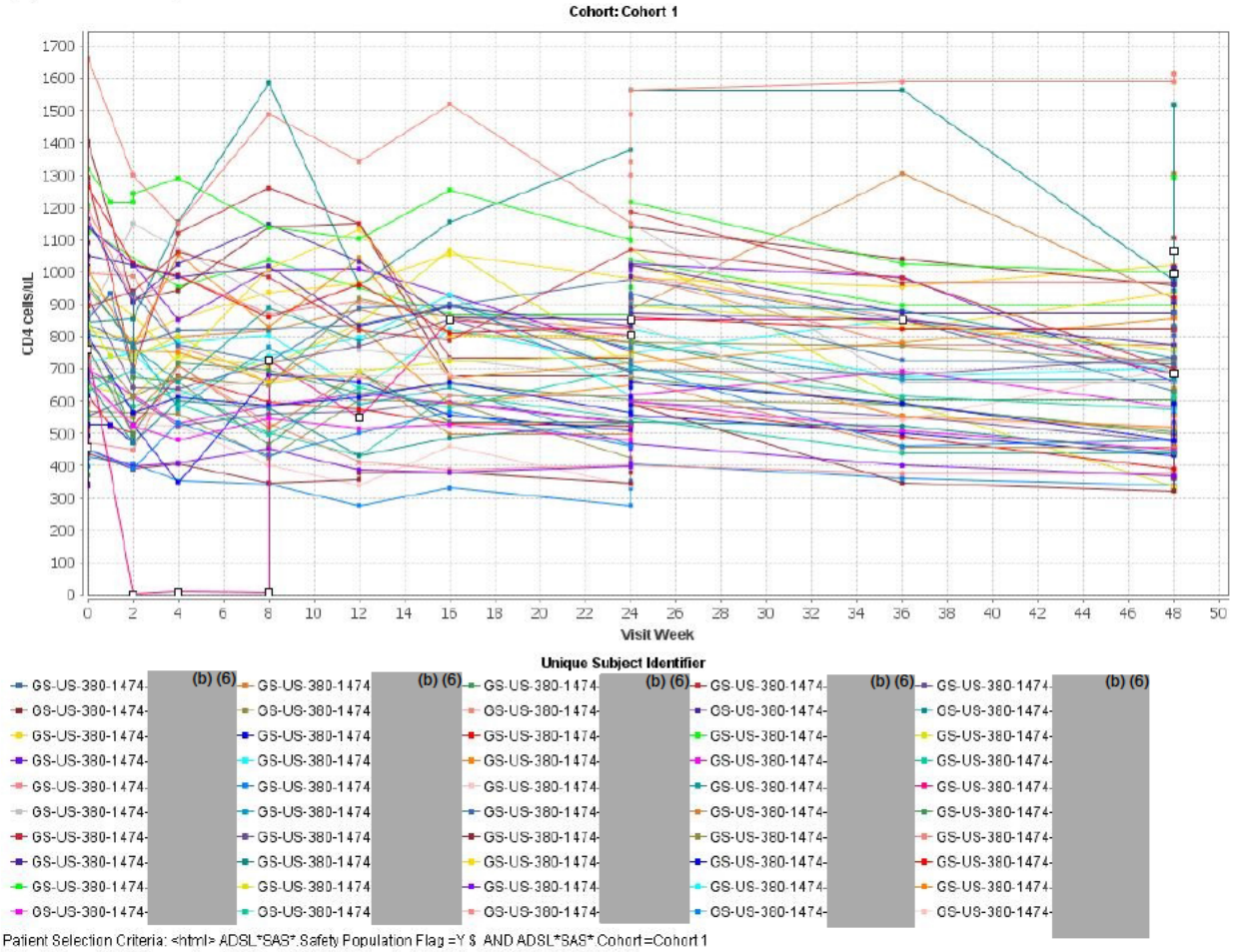


	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
Mean	929	933	906	924	911	912	902
Median	895	826	932	859	879	843	849
Q1	707	724	641	684	717	711	699
Q3	1121	1050	1038	1058	1039	1019	1015
Min	293	343	439	183	373	369	333
Max	2127	2198	2341	2248	2071	2566	1935
N	50	49	49	50	50	50	50

Source: ADEFF and ADLB datasets

Figure 7. Spaghetti Plot for Cohort 1 CD4+Cell Count Over 48 Weeks

Study: gs-us-380-1474 - Jun 4, 2019
Spaghetti Plot - Subset of patients

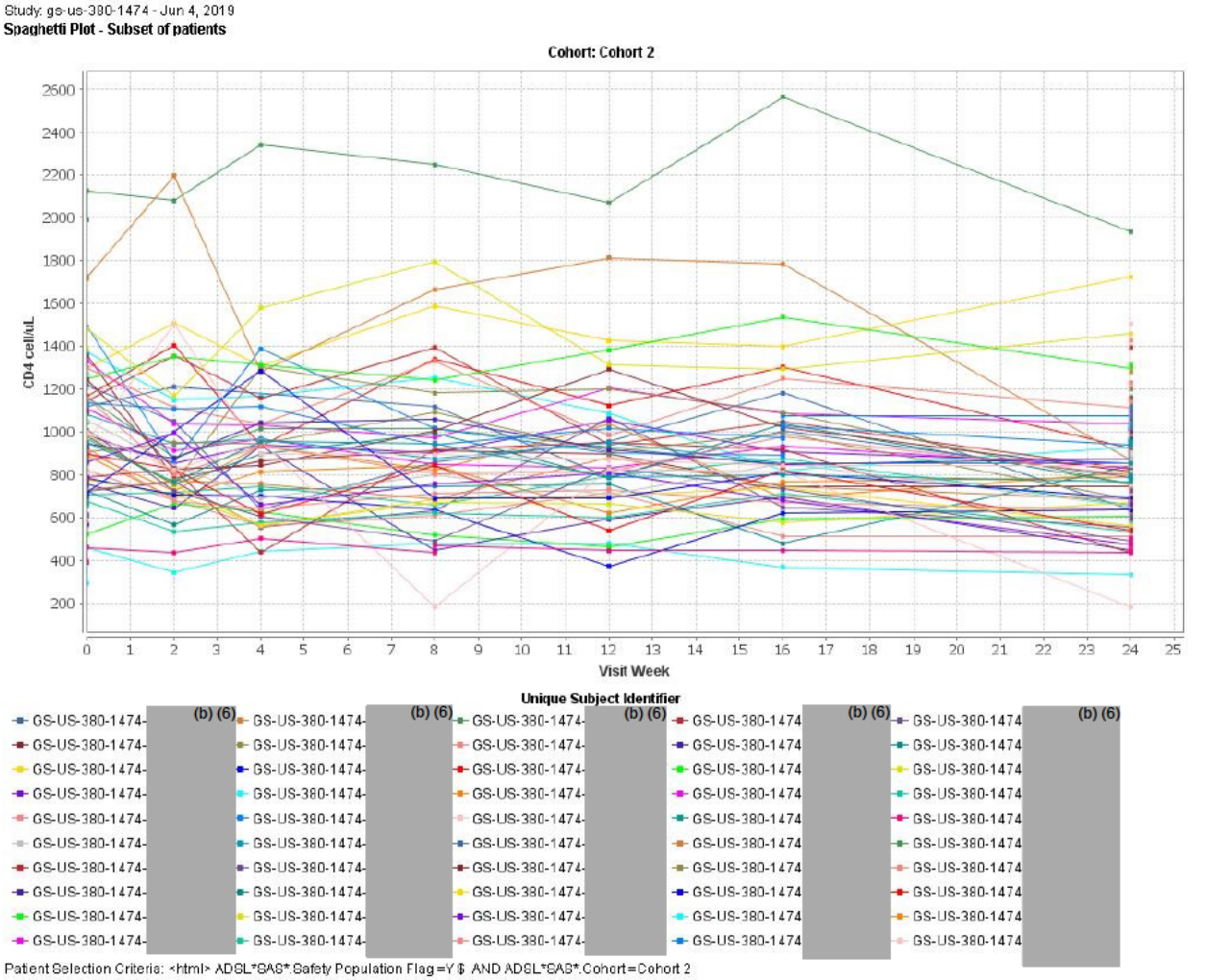


Patient Selection Criteria: <html> ADSL*SAS* Safety Population Flag =Y $ AND ADSL*SAS* Cohort=Cohort 1
Output Filter: ADEFF.Parameter=CD4 (/uL) AND ADLB.Analysis Visit N =0,1,2,4,8,12,16,24,36,48

Page 1 of 1

Source: Dr. Wendy Carter's analysis from ADLB dataset.

Figure 8. Spaghetti Plot for Cohort 2 CD4+Cell Count Over 24 Weeks



Source: Dr. Wendy Carter's analysis from ADLB dataset.

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/s/

TANVIR K BELL
06/06/2019 04:01:47 PM

WENDY W CARTER
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