



Biktarvy[®] (BIC/FTC/TAF) Use in Pediatric Patients

This document is in response to your request for information regarding the use of Biktarvy[®] (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) in pediatric patients with HIV-1.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Summary

Product Labeling¹

BIC/FTC/TAF is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥ 14 kg:

- with no ARV treatment history, or
- with an ARV treatment history and not VS, with no known or suspected substitutions associated with resistance to the INSTI class, FTC, or TFV, or
- to replace the current ARV regimen in those who are VS (HIV-1 RNA < 50 c/mL) on a stable ARV regimen with no known or suspected substitutions associated with resistance to BIC or TFV.

Clinical Data on BIC/FTC/TAF Use in Pediatric Participants

In an open-label study, Study 1474, the safety and efficacy of BIC/FTC/TAF treatment were evaluated in four cohorts of infants, children, and adolescents living with HIV-1.²⁻⁴

- In Cohorts 1 and 2, PK results were either similar to those seen in adults, or differences were not considered clinically significant. Through Week 96, five Grade 3/4 AEs were reported, and 1 participant experienced an AE that led to study drug discontinuation. Virologic suppression was maintained across both cohorts (99%; 95/96), with no treatment-emergent resistance through Week 96.^{2,3}
- In Cohort 3, participants were treated with BIC/FTC/TAF 30/120/15 mg STR, and BIC, FTC, and TAF exposures (AUC_{0-24}) in this population were generally consistent with the ranges of exposures observed in adults. Of the 22 participants who were included in this analysis, 18 experienced AEs of any grade through Week 48. No AEs were Grade 3 or 4, were serious, or led to study drug discontinuation. Virologic suppression was maintained through Week 96 in all participants (100%; 17/17).⁵
- In Cohort 4, participants were treated with BIC/FTC/TAF TOS of various strengths dosed by age and weight. Virologic suppression was generally maintained among participants who were VS on ART for ≥ 6 months at baseline (Group 1, 87.5%; 7/8) or was achieved among participants who were ARV naive or on ART for ≥ 1 month at baseline (range: 53.3–85.7%). Eight TRAEs (15.1%) were observed, and all were Grade 1; no serious or

Grade 3/4 TRAEs were reported. One participant experienced a TEAE that led to the discontinuation of study drug.⁴

In one pooled analysis of pediatric participants, 41% had ≥ 1 preexisting RAM, and virologic suppression rates were durable, including among participants with preexisting RAMs.^{6,7}

In another pooled analysis of pediatric participants who switched to FTC/TAF-based treatment, changes in weight, height, and BMI from baseline to Week 48 of BIC/FTC/TAF treatment were consistent with age-expected child development, and TC, LDL, and TG levels improved.^{8,9}

[Real-World Data on BIC/FTC/TAF Use in Pediatric Patients](#)

In a retrospective, single-center study of 74 pediatric patients receiving BIC/FTC/TAF 50/200/25 mg, 83.8% of patients were VS at the last study visit. Twenty-eight patients experienced VF, and 16 (57.1%) of those patients achieved virologic suppression by last visit with multifaceted interventions to improve adherence. One patient discontinued BIC/FTC/TAF due to a suspected AE, and 1 patient switched to a different ART regimen.¹⁰

Product Labeling¹

Dosage and Administration

Recommended dosage in adults and pediatric patients weighing ≥ 25 kg

The recommended dosage of BIC/FTC/TAF is one tablet containing 50 mg of BIC, 200 mg of FTC, and 25 mg of TAF taken orally once daily with or without food in adults and pediatric patients weighing ≥ 25 kg with an estimated CrCl ≥ 30 mL/min.

Recommended dosage in pediatric patients weighing ≥ 14 kg to < 25 kg

The recommended dosage of BIC/FTC/TAF 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 weighing ≥ 14 kg to < 25 kg with an estimated CrCl ≥ 30 mL/min.

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.

Use in Specific Populations

Pediatric use

The safety and effectiveness of BIC/FTC/TAF have been established as a complete regimen for the treatment of HIV-1 infection in pediatric patients weighing ≥ 14 kg:

- Who have no ARV treatment history, or
- With an ARV treatment history and not VS, with no known or suspected substitutions associated with resistance to the INSTI class, FTC, or TFV, or
- To replace the current ARV regimen in those who are VS (HIV-1 RNA < 50 c/mL) on a stable ARV regimen with no known or suspected resistance to BIC or TFV.

Use of BIC/FTC/TAF in pediatric patients weighing ≥ 14 kg is supported by the following:

- Trials in adults
- An open-label trial in three age-based cohorts of VS pediatric subjects:
 - Cohort 1: 12 to <18 years of age and weighing ≥ 35 kg receiving BIC/FTC/TAF through Week 48 (N=50),
 - Cohort 2: 6 to <12 years of age and weighing ≥ 25 kg receiving BIC/FTC/TAF through Week 24 (N=50), and
 - Cohort 3: ≥ 2 years of age and weighing ≥ 14 kg to <25 kg through Week 24 (N=22). No pediatric participants 2 years of age were enrolled; of the 6 participants who were 3 years of age at enrollment, 3 participants weighed between 14 to <15 kg.

The safety and efficacy of BIC/FTC/TAF in these pediatric participants were similar to that in adults, and there was no clinically significant change in exposure for the components of BIC/FTC/TAF.

Safety and effectiveness of BIC/FTC/TAF in pediatric patients weighing <14 kg have not been established.

Clinical Data on BIC/FTC/TAF Use in Pediatric Participants

Study GS-US-380-1474

Study design and demographics

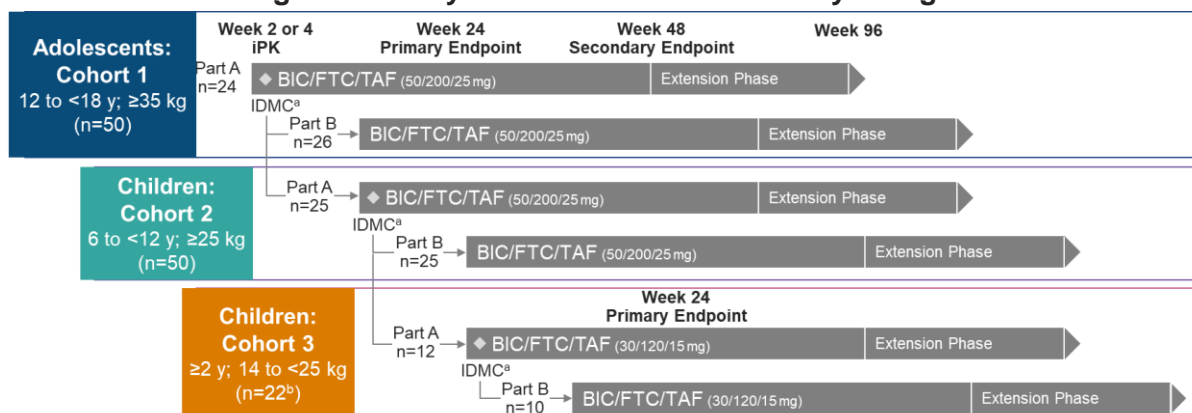
Study 1474 ([NCT02881320](#)) is an ongoing phase 2/3, single-arm, multicenter, multicohort, open-label clinical trial that is evaluating the PK, safety, tolerability, and efficacy of BIC/FTC/TAF in infants, children, and adolescents.²⁴

Cohorts 1 to 3²

VS adolescents aged 12 to <18 years (Cohort 1; n=50) and children aged 6 to <12 years (Cohort 2; n=50) with HIV-1 were enrolled and received BIC/FTC/TAF 50/200/25 mg STR. Participants from Cohorts 1 and 2 were enrolled in two groups: Part A (Cohort 1, n=24 and Cohort 2, n=25) assessed PK and confirmed dosing of BIC/FTC/TAF, and Part B assessed the safety and efficacy of BIC/FTC/TAF (Figure 1). Cohort 3 consisted of children with HIV-1 who were aged ≥ 2 years. This cohort was treated with a BIC/FTC/TAF 30/120/15 mg STR (60% of full strength).

For Cohorts 1 to 3, participants were switched from their current, stable ARV regimen of two NRTIs plus a third agent to BIC/FTC/TAF. Key inclusion criteria were HIV-1 RNA <50 c/mL for ≥ 6 months prior to screening, CD4 count ≥ 200 cells/mL, and $eGFR_{\text{Schwartz}} \geq 90$ mL/min/1.73 m². The primary objectives were an assessment of PK parameters (AUC_T and C_T) of BIC at steady state at Weeks 2 and 4 (Cohorts 1 and 2) and safety and tolerability of BIC/FTC/TAF through Week 24. Secondary objectives included assessment of the safety and tolerability of BIC/FTC/TAF through Week 48, the proportion of participants with HIV-1 RNA <50 c/mL by FDA Snapshot analysis at Weeks 24 and 48, assessment of PK parameters (C_{max} and T_{max} for BIC and AUC_T , C_{max} , and C_T for FTC and TAF), and the change from baseline and percentage change in CD4 counts at Weeks 24 and 48.

Figure 1. Study 1474 Cohorts 1 to 3: Study Design²



Abbreviation: IDMC=Independent Data Monitoring Committee.

^aIDMC reviewed data once 50% of participants reached Week 12 and once all participants completed the iPK visit (Week 2 or 4).

^bSix participants switched treatment to adult-strength BIC/FTC/TAF once they weighed >25 kg.

Table 1. Study 1474 Cohorts 1 to 3: Baseline Demographics and Disease Characteristics^{2,5}

Key Demographics and Characteristics	Cohort 1: Adolescents (n=50)	Cohort 2: Children 6 to <12 Years (n=50)	Cohort 3: Children ≥2 Years (n=22)
Age, median (range), years	15 (12–17)	10 (6–11)	6 (3–7) ^a
Weight, median (IQR), kg	44.8 (40–56.1)	29 (26.9–32.5)	18.7 (15.2–21.7)
Female, n (%)	32 (64)	27 (54)	11 (50)
Race, Black/Asian/White, n (%)	32 (65)/13 (27)/1 (2)	36 (72)/11 (22)/2 (4)	16 (73)/5 (23)/0 ^b
CD4 count, median (IQR), cells/mcL	750 (586–926)	898 (707–1121)	962 (748–1419)
eGFR _{Schwartz} , median (IQR), mL/min/1.73 m ²	145 (134–170)	153.5 (144–173)	160.5 (145–168)
Vertical transmission, n (%)	45 (90)	48 (96)	22 (100)

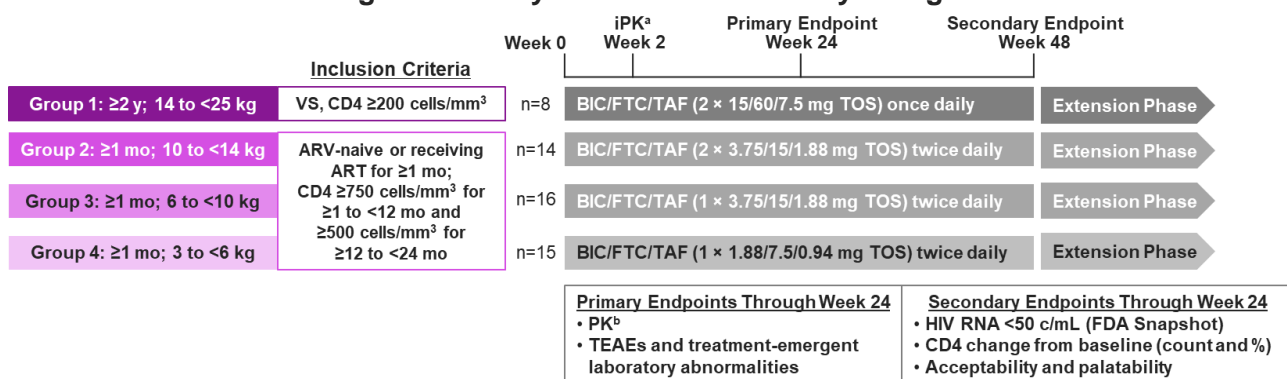
^aMedian (IQR). ^bBlack/Asian race reported; 1 participant had “other” race.

Cohort 4⁴

Cohort 4 consisted of children with HIV-1 aged ≥1 month to ≥2 years of age who weighed 3 kg to <25 kg. Participants in Cohort 4 were stratified into four groups and treated with various strengths of BIC/FTC/TAF TOS.

Eligible participants had an eGFR ≥90 mL/min/1.73 m² for children aged ≥1 year (or adequate renal function for those <1 year of age, defined as an eGFR_{Schwartz} ≥ the minimal value for the normal adjusted eGFR by age) and did not have active hepatitis B or C infection. Participants enrolled in Group 1 were VS on ART for ≥6 months, and those enrolled in Groups 2 to 4 were ARV naive or had been receiving ART for ≥1 month (Figure 2). Primary study endpoints at Week 24 included PK and safety. All participants had asymptomatic HIV acquired via vertical transmission (Table 2).

Figure 2. Study 1474 Cohort 4: Study Design⁴



^aiPK assessments were performed for Groups 2 to 4. ^bData not presented.

Table 2. Study 1474 Cohort 4: Baseline Demographics and Disease Characteristics⁴

Key Demographics and Characteristics	Group 1: Children ≥2 Years and 14 to <25 kg (n=8 ^a)	Group 2: Infants ≥1 Month and 10 to <14 kg (n=14 ^b)	Group 3: Infants ≥1 Month and 6 to <10 kg (n=16 ^c)	Group 4: Infants ≥1 Month and 3 to <6 kg (n=15 ^d)
Age, median (range)	4 (2–7) years	2 (1–4) years	8 (2–19) months	4 (2–16) months
Weight, median (range), kg	15.9 (14.1–18.8)	11.3 (10–13.8)	8 (6–9.6)	5.4 (4.6–5.9)
Female sex at birth, n (%)	3 (37.5)	8 (57.1)	11 (68.8)	9 (60)
Black race, n (%)	7 (87.5)	14 (100)	14 (87.5)	15 (100)
HIV-1 RNA, median (range), log ₁₀ c/mL	1.3 (1.3–1.4)	1.7 (1.3–2.5)	1.6 (1.3–4.8)	2.6 (1.3–6.9)
CD4, median (Q1, Q3)	Cells/mcL	932 (604, 1254)	1573 (1126, 1987)	2310 (1742, 2595)
	%	38.3 (31.7, 42.9)	33.6 (31.6, 35.7)	34.9 (27.6, 39.3)
eGFR, median (Q1, Q3), mL/min/1.73 m ²	173 (150, 179)	151 (136, 158)	127 (110, 166)	109 (97, 111)

^aCountries of origin were as follows: South Africa, n=5; Uganda, n=2; and US, n=1.

^bCountries of origin were as follows: Uganda, n=12 and South Africa, n=2.

^cCountries of origin were as follows: Uganda, n=10; South Africa, n=4; and US, n=2.

^dCountries of origin were as follows: Uganda, n=14 and South Africa, n=1.

PK results

Cohort 1 (adolescents)²

The BIC C_T in adolescents was 35% lower than what was observed in adults in phase 3 clinical trials. FTC and TAF exposures (AUC_T) in adolescents were similar to those observed in adults in phase 3 clinical trials and were within the known safety ranges of historical data in adults and adolescents following administration of approved FTC/TAF-containing products (Table 3).

Table 3. Study 1474 Cohort 1 (Adolescents, Part A): Summary of PK Parameters²

PK Parameter, Mean (CV)	Cohort 1 Adolescents	BIC/FTC/TAF-Treated Adults ^a	Adolescent/Adult GLSM ^b (90% CI)
n	50	1193	–
AUC _T , h·ng/mL	89,100 (31)	102,000 (26.9)	86.3 (80–93)
C _{max} , ng/mL	6240 (27.1)	6150 (22.9)	100 (93.8–107)
C _T , ng/mL	1780 (44.4)	2610 (35.2)	65.4 (58.3–73.3)

PK Parameter, Mean (CV)		Cohort 1 Adolescents	BIC/FTC/TAF-Treated Adults ^a	Adolescent/Adult GLSM ^b (90% CI)
FTC ^d	n	24	77	–
	AUC _T , h·ng/mL	13,600 (21.7)	12,300 (29.2)	113 (102–124)
	C _{max} , ng/mL	2690 (34)	2130 (34.7)	127 (111–145)
	C _T , ng/mL	64.4 (25)	96 (37.4) ^e	69.3 (61.6–77.9)
TAF ^c	n	49	486	–
	AUC _T , h·ng/mL	196 (50.3)	142 (17.3)	128 (116–141)
	C _{max} , ng/mL	133 (70.2)	121 (15.4)	88.6 (75–105)

^aPooled population PK data from four phase 3 studies in adult PWH.

^bReported as ratio of test to reference.

^cCohort 1 (adolescent) data were obtained from population PK data.

^dCohort 1 (adolescent) data were obtained from the intensive PK substudy (Part A).

^en=74.

Cohort 2 (children)²

BIC exposures (AUC_T and C_T) in children were within the predefined PK boundaries and consistent with the ranges of BIC exposures observed in adults in phase 3 clinical trials of BIC/FTC/TAF, although BIC C_T was 11% lower in children than in adults. Mean FTC and TAF exposures (AUC_T) were higher in children than in adults but were within known safety ranges of historical data in adults and children (Table 4).

Table 4. Study 1474 Cohort 2 (Children, Part A): Summary of PK Parameters²

PK Parameter, Mean (CV)		Cohort 2: Children, Part A	BIC/FTC/TAF-Treated Adults ^a	Children/Adult GLSM ^b (90% CI)
BIC ^c	n	50	1193	–
	AUC _T , h·ng/mL	128,000 (27.8)	102,000 (26.9)	125 (117–134)
	C _{max} , ng/mL	9460 (24.3)	6150 (22.9)	153 (143–163)
	C _T , ng/mL	2360 (39)	2610 (35.2)	88.9 (80.6–98)
FTC ^d	n	25	77	–
	AUC _T , h·ng/mL	17,600 (36.9)	12,300 (29.2)	143 (127–159)
	C _{max} , ng/mL	3890 (31)	2130 (34.7)	185 (162–210)
	C _T , ng/mL	227 (322.8) ^e	96 (37.4) ^f	95 (69.9–129)
TAF ^c	n	47	486	–
	AUC _T , h·ng/mL	278 (40.3)	142 (17.3)	183 (165–202)
	C _{max} , ng/mL	205 (44.6)	121 (15.4)	153 (136–173)

^aPooled population PK data from four phase 3 studies in adult PWH.

^bReported as ratio of test to reference.

^cCohort 2 (children) data were obtained from population PK data.

^dCohort 2 (children) data were obtained from the intensive PK substudy (Part A).

^en=24. ^fn=74.

Cohort 3 (children ≥2 years)⁵

Cohort 3 consisted of children aged ≥2 years who weighed between 14 and <25 kg who were treated with BIC/FTC/TAF 30/120/15 mg STR. Intensive PK sampling illustrated that BIC exposures (AUC_T and C_{max}) in children who weighed 14 to 25 kg were within the PK equivalence ranges of BIC exposures observed in adults (Table 5). Although C_T in children was lower than that observed in adults, it was still approximately 12-fold greater than the protein-adjusted 95% effective concentration (162 ng/mL) against wild-type HIV-1 virus. Although the 90% CIs for some FTC and TAF exposure parameters fell outside of the equivalence boundaries, exposure parameters in this population were generally consistent with the known efficacy and safety ranges of historical data in adults and children (Table 5).

Table 5. Study 1474 Cohort 3 (Children, Part A): Summary of PK Parameters⁵

PK Parameter, GLSM		Cohort 3 (n=12) ^a	BIC/FTC/TAF-Treated Adults ^b	Children/Adult GLSM Ratio, (90% CI) ^c
BIC	AUC _T , h·ng/mL	105,892	98,430	107.6 (96.7–119.7)
	C _{max} , ng/mL	9856.7	5986.1	164.7 (149.5–181.4)
	C _T , ng/mL	1604.8	2453	65.4 (49.1–87.2)
FTC	AUC _T , h·ng/mL	14,708.4	11,789.5	124.8 (111.8–139.2)
	C _{max} , ng/mL	3629.6	2004	181.1 (150.1–218.5)
	C _T , ng/mL	74.3	89.9	82.6 (47.7–143.1)
TAF	AUC _T , h·ng/mL	281.7	194.6	144.7 (114.9–182.2)
	C _{max} , ng/mL	392.8	227.2	172.9 (139.8–213.8)
	AUC _{last} , h·ng/mL	279.7	192.5	145.3 (115.3–183.1)

Abbreviation: AUC_{last}=area under the curve up to the last measurable concentration.

^aOne participant had missing BIC and FTC PK data for C_T.

^bPooled PK data from four phase 3 studies in adult PWH; n=1193 for BIC and n=74 to 77 for FTC and TAF reference PK data.

^cPK equivalence was met if the 90% CIs of the GLSM ratio were within the predefined equivalence boundary of 50 to 200%.

Cohort 4 (children ≥2 years and infants ≥1 month)⁴

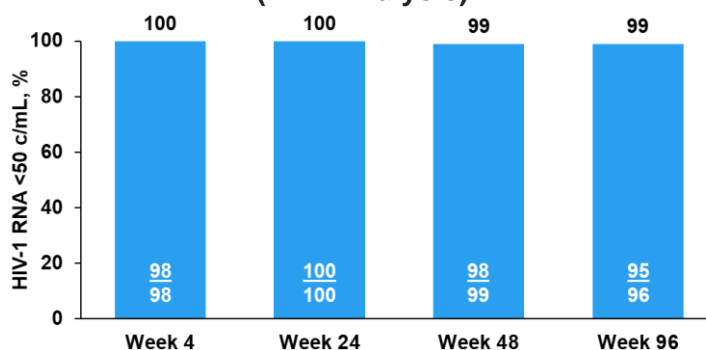
No PK data have been presented.

Efficacy and safety results

Cohorts 1 and 2: pooled efficacy results through Week 96

High rates of virologic suppression (HIV-1 RNA <50 c/mL) were maintained with BIC/FTC/TAF through Week 96 with no treatment-emergent resistance (Figure 3).³ The mean changes from baseline in CD4 count between Weeks 2 and 48 ranged from -40 to +56 cells/mcL. Two participants met the criteria for resistance testing at Week 48, and no emergent resistance was reported. Three participants had a resistance mutation to FTC at baseline and maintained virologic suppression through Week 48.²

Figure 3. Study 1474 Cohorts 1 and 2: Virologic Suppression Through Week 96 (M=E Analysis)³



Cohorts 1 and 2: pooled safety results through Week 96

Of the 100 participants included in this analysis, 86% experienced AEs of any grade (Table 6). AEs deemed study drug-related by investigators and occurring in >1 participant included abdominal discomfort (n=3) and transient neutropenia (n=2).³ One 7-year-old female participant with a past medical history of anxiety and neuropsychiatric changes experienced Grade 2 insomnia and anxiety at Week 20; this was considered to be

treatment-related by the investigator, and the participant discontinued the study.² Thirty participants experienced treatment-emergent Grade 3 or 4 laboratory abnormalities, with the most frequent being hematuria (16%). Between Weeks 1 and 96, the median change in eGFR_{Schwartz} was -15.5 mL/min/1.73 m².³

Table 6. Study 1474 Cohorts 1 and 2: Safety Outcomes at Week 96³

		Cohorts 1 and 2 (n=100)
Exposure to study drug, median (IQR), weeks		151.4 (125.6–153.5)
Any AE, n (%)		86 (86)
Any-grade AE in ≥10% in either group, n (%)	URTI	30 (30)
	Cough	15 (15)
	Diarrhea	11 (11)
	Headache	11 (11)
	Nasopharyngitis	11 (11)
Vomiting		8 (8)
AEs related to study drug, n (%)		13 (13)
Grade 3–4 AEs, n (%)		5 (5)
SAEs, n (%)		5 (5)
AEs that led to study drug discontinuation, ^a n (%)		1 (1)
Death, n		0

^aDiscontinuation due to Grade 2 insomnia and anxiety in Cohort 2.

From baseline to Week 48, slight changes in height and weight Z-scores were observed (Table 7).²

Table 7. Study 1474 Cohorts 1 and 2: Changes From Baseline in Height and Weight Z-Scores^{11a}

Median (IQR)			Cohort 1: Adolescents (n=50)	Cohort 2: Children (n=50)	Cohorts 1 and 2 (n=100)
Height	Baseline		-0.97 (-1.62 to -0.41)	-0.67 (-1.27 to 0.01)	-0.8 (-1.47 to -0.14)
	Change from baseline	Week 24	0.05 (-0.06 to 0.2)	0.01 (-1.13 to 0.14)	0.04 (-0.09 to 0.16)
		Week 48	0.04 (-0.08 to 0.18)	0.02 (-0.21 to 0.24)	0.2 (0.04–1.1)
Weight	Baseline		-0.54 (-1.55 to 0.39)	-0.35 (-1.3 to 0.45)	-0.45 (-1.5 to 0.4)
	Change from baseline	Week 24	0.09 (-0.03 to 0.31)	0.23 (0.09–0.48)	0.21 (0–0.43)
		Week 48	0.17 (-0.15 to 0.41)	0.33 (0.11–0.64)	0.27 (-0.01 to 0.51)

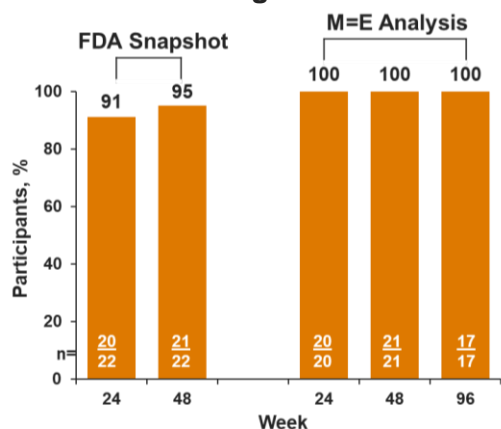
^aZ-scores generated based on growth charts from year 2000 on the US CDC website.

At Day 1 and Week 4, 100% of participants (100/100) reported that BIC/FTC/TAF was palatable, and its shape and size were acceptable. Median adherence by pill count was 99% through Weeks 24 and 48 and 98% through Week 96.³

Cohort 3: efficacy results through Week 96⁵

Virologic suppression (HIV-1 RNA <50 c/mL) was maintained through Week 96 in all participants, as assessed using an M=E analysis (Figure 4), and the median CD4 change from baseline was -137 cells/mcL.

Figure 4. Study 1474 Cohort 3: Virologic Suppression (HIV-1 RNA <50 c/mL) Through Week 96⁵



Cohort 3: safety and tolerability results through Week 48

As of data cutoff, 11 participants had switched to full-dose BIC/FTC/TAF after reaching a weight of ≥ 25 kg; these participants were included in the safety analyses. Of the 22 participants included in this analysis, no participants experienced any Grade 3 to 4 AEs or SAEs, and no participants discontinued the study drug due to an AE.⁵

Table 8. Study 1474 Cohort 3: Safety Outcomes at Week 48⁵

Safety Outcome		Cohort 3 (n=22)
Study drug exposure duration, median (IQR), weeks		99.5 (73.9–108.1)
Any AE, n (%)		18 (82)
Any-grade AE in $\geq 10\%$, n (%)	URTI	7 (32)
	Cough	5 (23)
	Diarrhea	3 (14)
	Nasopharyngitis	3 (14)
	Nausea	3 (14)
	Vomiting	3 (14)
AEs related to study drug, n (%)		3 (14) ^a
Grade 3–4 laboratory abnormalities, n (%)		6 (27) ^b

^aNeutropenia (n=1); abdominal pain, constipation, and nausea (n=1); irritability, social avoidant behavior, and weight increase (n=1). All AEs related to study drug were Grade 1 or 2.

^bThe only Grade 3 to 4 laboratory abnormality that occurred in >1 participant was decreased neutrophils (n=4); all events of decreased neutrophils were transient.

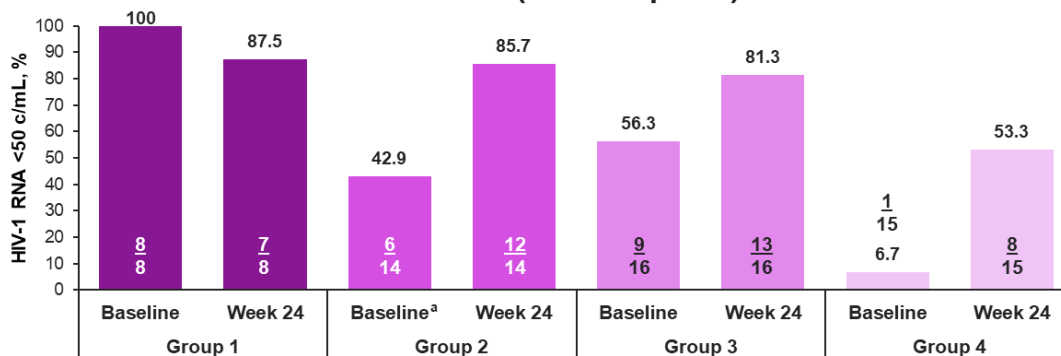
At Week 96, the median change in eGFR_{Schwartz} was -7.5 mL/min/1.73 m². Changes in eGFR_{Schwartz} in this cohort were consistent with the known effects of BIC on the renal creatinine transporter. These changes were not considered clinically significant.¹²

Through Week 48, tablet acceptability and palatability were generally high, with $\geq 79\%$ of those who swallowed the tablets whole reporting them as “easy” or “super easy” to swallow and $\geq 91\%$ of participants describing the tablets as neutral or positive at palatability assessments. Median adherence by pill count was 99%.⁵

Cohort 4: efficacy results through Week 24⁴

By FDA Snapshot analysis, the overall virologic suppression rate was 75.5% (40/53) at Week 24; virologic suppression rates by group are shown in Figure 5.

Figure 5. Study 1474 Cohort 4: Virologic Suppression (HIV-1 RNA <50 c/mL) at Baseline and Week 24 (FDA Snapshot)⁴



^aBaseline data were missing for 1 participant in Group 2, who was included in the denominator.

The overall median change in CD4 count and percentage change from baseline to Week 24 were within the expected range of fluctuation for this age group.

Cohort 4: safety and tolerability results through Week 24⁴

Overall, nearly all participants (96.2%; 51/53) reported a TEAE; 8 (15.1%) reported a TRAE, and each TRAE was Grade 1 in severity. No serious or Grade 3/4 TRAEs were reported. Nearly one-third of participants (32%; 17/53) experienced a Grade 3 or 4 laboratory abnormality; increases in amylase levels were not associated with lipase level increases or pancreatitis, returned to baseline levels at follow-up, and did not require BIC/FTC/TAF interruption.

Table 9. Study 1474 Cohort 4: Safety Outcomes Through Week 24⁴

Safety Outcomes		Group 1: Children ≥2 Years and 14 to <25 kg (n=8)	Group 2: Infants ≥1 Month and 10 to <14 kg (n=14)	Group 3: Infants ≥1 Month and 6 to <10 kg (n=16)	Group 4: Infants ≥1 Month and 3 to <6 kg (n=15)
Exposure to study drug, median (IQR), weeks		97.4 (71.5–108.8)	107 (82.1–114.1)	70.5 (62.4–97.3)	48.1 (31.1–63.1)
Any TEAE, n (%)		8 (100)	13 (92.9)	15 (93.8)	15 (100)
TRAE, n (%)		2 (25) ^a	0	2 (12.5) ^b	4 (26.7) ^c
TEAE that led to study drug discontinuation, n (%)		1 (12.5) ^d	0	0	0
Death, n (%)		0	0	0	1 (6.7) ^e
Most common ^f Grade 3 or 4 laboratory abnormalities, n (%)	Amylase increased	1 (12.5)	1 (7.1)	5 (31.3)	3 (20)
	Neutrophils decreased	1 (12.5)	0	1 (6.3)	2 (13.3)
	ALP increased	0	1 (7.1)	0	2 (13.3)
	Hypomagnesemia	0	0	3 (18.8)	0

Abbreviation: ALP=alkaline phosphatase.

^aVomiting and ALT increased and amylase increased (each, n=1).

^bVomiting and pruritus (each, n=1). ^cVomiting (n=4).

^dPulmonary tuberculosis; unrelated to BIC/FTC/TAF. ^ePneumonia; unrelated to BIC/FTC/TAF.

^fOccurred in ≥3 participants.

From baseline to Week 24, no clinically significant changes in height/length and weight Z-scores and eGFR measurements were observed (eGFR variations were within the expected range of changes by age; Table 10).

Table 10. Study 1474 Cohort 3: Baseline and Week 24 Height/Length and Weight Z-Scores^a and eGFR

Parameter, Median		Group 1: Children ≥2 Years and 14 to <25 kg	Group 2: Infants ≥1 Month and 10 to <14 kg	Group 3: Infants ≥1 Month and 6 to <10 kg	Group 4: Infants ≥1 Month and 3 to <6 kg
Height/length Z-score	Baseline	-0.37	-2	-0.88	-2.2
	Week 24	-0.57	-1.74	-1.05	-2.37
Weight Z-score	Baseline	-0.67	-1.46	-0.82	-2.04
	Week 24	-0.67	-1.32	-0.93	-2.14
eGFR, mL/min/1.73 m ²	Baseline	173	151	127	109
	Week 24	147	140	137	127

^aZ-scores generated based on growth charts from year 2000 on the US CDC website for participants aged ≥24 months and World Health Organization growth charts for those aged <24 months.

Over the course of the study, caregivers of study participants reported a neutral or favorable rating for palatability and acceptability, with 42.9% of the 49 caregivers with available data reporting a rating of “super good” and 46.9% reporting “good” palatability at Week 24. At Week 24, 98% of the 51 caregivers with available data reported that the entire dose was successfully administered to the participants.

Pooled Analysis of Resistance to FTC/TAF-Based Regimens in Pediatric Studies

Study design and demographics⁶

A pooled analysis of four studies (N=341) assessed preexisting drug resistance, treatment-emergent resistance, and the impact of resistance on long-term efficacy of FTC/TAF-based treatment in pediatric populations. Studies included were GS-US-380-1474 (summarized above; BIC/FTC/TAF), GS-US-292-0106 (E/C/F/TAF), GS-US-292-1515 (E/C/F/TAF), and GS-US-311-1269 (FTC/TAF + third agent; Figure 6). Data for BIC/FTC/TAF-treated participants are summarized below.

Participants received an FTC/TAF-based regimen for a median duration of 157 weeks. In the pooled study population, the median (IQR) age was 12 (9–15) years; 52% of participants were aged 12 to <18 years, 42% were aged 6 to <12 years, and 6% were aged 2 to <6 years. Fifty-eight percent of participants were female, 75% were Black, 15% were ARV naive, and 85% were VS.

Figure 6. Pooled Analysis of Resistance: Study Design⁶

GS-US-380-1474	Cohort 1: 12 to <18 y; ≥35 kg; VS	n=50	BIC/FTC/TAF 50/200/25 mg	Baseline Genotypic Analyses -In ARV-naive participants, prospective HIV -1 RNA genotyping -If available, historical HIV -1 genotypes and retrospective HIV -1 proviral DNA genotyping (VS participants) Resistance Analysis Population -Participants with HIV -1 RNA ≥200 c/mL (BIC/FTC/TAF) or ≥400 c/mL (E/C/F/TAF or FTC/TAF + third agent) at confirmed VF ^b or at last on-treatment visit Efficacy Analysis Population -Participants with ≥1 on-treatment HIV -1 RNA measurement -Virologic outcomes were based on last on-treatment HIV-1 RNA level (LOCF): <50 c/mL (suppressed) or ≥50 c/mL (not suppressed)
	Cohort 2: 6 to <12 y; ≥25 kg; VS	n=50	BIC/FTC/TAF 50/200/25 mg	
	Cohort 3: ≥2 y; ≥4 to <25 kg; VS	n=22	BIC/FTC/TAF 30/120/15 mg	
GS-US-292-0106	Cohort 1: 12 to <18 y; ≥35 kg; ARV-naive	n=50	E/C/F/TAF 150/150/200/10 mg	
	Cohort 2: 6 to <12 y; ≥25 kg; VS	n=52	E/C/F/TAF 150/150/200/10 mg	
	Cohort 3: ≥2 y; ≥14 to <25 kg; VS	n=27	E/C/F/TAF 90/90/120/6 mg	
GS-US-292-1515	12 to <18 y; ≥35 kg; VS	n=50	E/C/F/TAF 150/150/200/10 mg	
GS-US-311-1269	Cohort 1: 12 to <18 y; ≥35 kg; VS	n=28	FTC/TAF ^a + third agent	
	Cohort 2, Group 1: 6 to <12 y; ≥25 kg; VS	n=9	FTC/TAF ^a + third agent	
	Cohort 2, Group 2: ≥2 to 12 y; 17 to <25 kg; VS	n=3	FTC/TAF ^a + third agent	

Abbreviation: LOCF=last observation carried forward.

^aIn Cohort 1, FTC/TAF was dosed as 200/25 mg if unboosted and 200/10 mg if boosted; in Cohort 2, Group 1, FTC/TAF was dosed as 200/25 mg if boosted or unboosted; in Cohort 2, Group 2, FTC/TAF was dosed as 120/15 mg if boosted or unboosted.

^bConfirmed VF was defined as HIV-1 RNA ≥50 c/mL at two consecutive study visits or last on-treatment visit.

Resistance results: participants who received BIC/FTC/TAF⁶

Baseline resistance

Forty-one percent of participants (39/95) who had resistance data at baseline had ≥1 preexisting RAM (Table 11).

Table 11. Pooled Analysis of Resistance: Baseline Resistance Data in BIC/FTC/TAF-Treated VS Participants^{6,7}

Participants With Baseline Resistance Data, n/N (%)	BIC/FTC/TAF (n=122)
Any baseline resistance ^a	39/95 (41)
NRTI-R	17/95 (18)
M184V/I	11/95 (12)
Any TAM	12/95 (13)
K65R	1/95 (1) ^b
NNRTI-R	28/95 (59)
K103N	6/95 (6)
PI-R	11/95 (11)
INSTI-R	6/92 (7)
E92G	2/92 (2)
T97A	2/92 (2)
Y143C	1/92 (1)
R263K	1/92 (1)

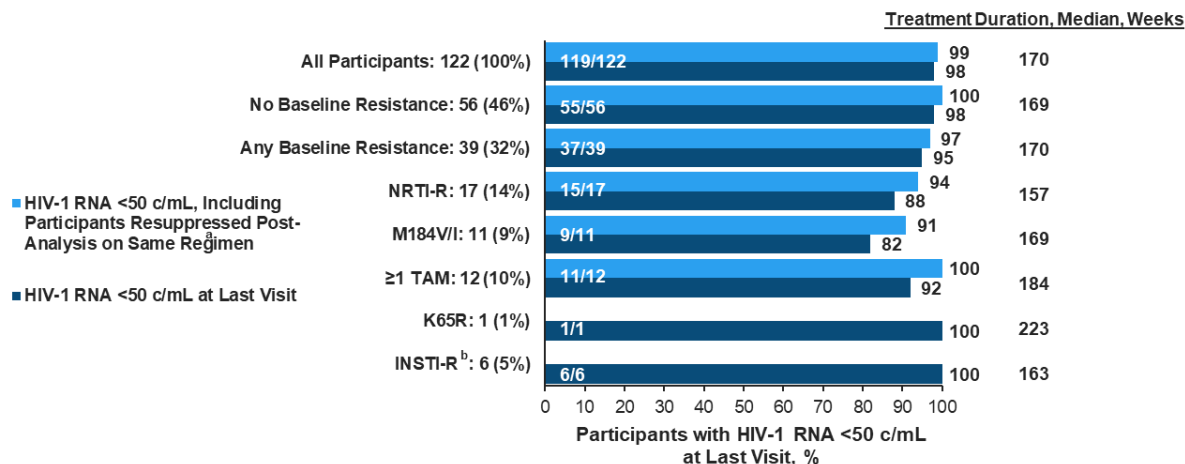
Abbreviations: NNRTI-R=non-nucleos(t)ide reverse transcriptase inhibitor resistance; PI-R=protease inhibitor resistance.

^aThose without integrase resistance data were considered as having no INSTI RAM.

^bThis participant maintained virological suppression through Week 223 of BIC/FTC/TAF treatment.

Virologic suppression rates by treatment regimen and baseline resistance showed a durable response; rates for those treated with BIC/FTC/TAF are shown in Figure 7.

Figure 7. Pooled Analysis of Resistance: Virologic Suppression Among BIC/FTC/TAF-Treated Participants at Last Visit by Baseline Resistance⁶



^aThis group consisted of participants who were resuppressed on the same ARV regimen and had additional follow-up data after the data cut date, and who completed the study and continued to receive their regimen.

^bINSTI-R included E92G and T97A (each, n=2); R263K and Y143C (each, n=1).

Post-baseline resistance

Eight of the 122 participants (7%) treated with BIC/FTC/TAF within the resistance analysis population underwent evaluation for the development of resistance. Seven of the 8 participants (88%) were resuppressed without a change in study ARV regimen; no treatment-emergent RAMs were detected.

Pooled Analysis of VS Pediatric Participants Who Switched to FTC/TAF-Based Regimens

Study design and demographics⁸

A pooled analysis of two Gilead studies assessed the impact of switching to an FTC/TAF-based ARV regimen in VS pediatric PWH who were ≥2 years of age and weighed 14 to <25 kg (N=49). All participants had switched from INSTI-, NNRTI-, or PI-based ARV regimens within the following studies: GS-US-380-1474 (summarized above; n=22; switched to BIC/FTC/TAF 30/120/15 mg) and GS-US-292-0106 (summarized above; n=27; switched to E/C/F/TAF 90/90/120/6 mg). Outcomes included changes from baseline to Week 48 in weight, height, BMI, and lipid panel parameters. Data for BIC/FTC/TAF-treated participants are summarized below.

Of the 22 BIC/FTC/TAF-treated participants, the median (IQR) age was 6 (3–7) years; 11 participants were female, 16 were Black, and 5 were Asian. The median (IQR) CD4 count was 962 (748, 1419) cells/mcL, and the median (IQR) CD4% was 32% (29.3–37.2%). All participants were previously treated with an NRTI (ABC, n=18; 3TC, n=17; non-ABC-based, n=5), and 9 were previously treated with efavirenz.

Results: participants who switched to BIC/FTC/TAF

Weight, height, and BMI Z-scores changed from baseline to Week 48 at rates that were consistent with growth expectations for participant age, and the BMI-for-age percentile increased by 4.2%.^{8,9} From baseline to Week 48, percentages of participants who were

underweight decreased from 13.6% to 9.1%, respectively, and rates of those with normal weight increased from 63.6% to 68.2%, respectively; rates of those who were overweight or obese remained stable at 22.7% at each time point. In a multivariate linear regression of the entire study population (N=49), being female ($P=0.0213$), and being underweight at baseline ($P=0.0248$) were factors that were associated with a greater change in the BMI-for-age percentile at Week 48.⁹

Among BIC/FTC/TAF-treated participants with lipid panel measurements (n=21), from baseline to Week 48, the percentage of participants of those who had acceptable TC (42.9% to 85.7%, respectively), LDL (47.6% to 76.2%, respectively), and TG (47.6% to 76.2%, respectively) levels increased. The rates of acceptable HDL levels decreased during this time period from 76.2% to 52.4%, respectively. Of the 5 participants who were categorized as overweight or obese at baseline, the following trends in lipid panel measurements were noted at baseline and Week 48: 2 and 0 participants, respectively, had borderline high or high TC; 2 and 2 participants had borderline high or high LDL; 4 and 0 participants had borderline high or high TG; 2 and 4 participants had borderline low or low HDL. Median (IQR) changes from baseline to Week 48 in lipid parameters were as follows: TC, -25 (-46 to -7) mg/dL; LDL, -21 (-43 to -3) mg/dL; TG, -16 (-47 to -1) mg/dL; HDL, -8 (-11 to 1) mg/dL.⁹

Real-World Data on BIC/FTC/TAF Use in Pediatric Patients

Retrospective, Single-Center Study in France¹⁰

Study design and demographics

A retrospective, single-center study in France was conducted to assess the safety and effectiveness of treatment with BIC/FTC/TAF 50/200/25 mg for ≥ 6 months in children and adolescents with HIV-1 who weighed ≥ 25 kg. VF was defined as the inability to attain HIV-1 RNA < 50 c/mL within 6 months of BIC/FTC/TAF treatment or the occurrence of virologic rebound (2 consecutive HIV-1 RNA values ≥ 50 c/mL) among patients who had previously achieved virologic suppression. Genotypic resistance testing was performed for any patient who experienced VF. Among the 74 patients included in the study, the overall median (IQR) age was 11.2 (8.8–15.2) years, 67.6% of all patients were VS (HIV-1 RNA < 50 c/mL) on ART, 93.2% were ARV experienced (median duration of exposure, 7.2 years), and most (85.1%) had previously been exposed to INSTIs (primarily dolutegravir).

Results

At a median (IQR) follow-up duration of 40 (21–46) months in the overall population, 62 patients (83.8%) had HIV-1 RNA < 50 c/mL without ART changes at their last visit, and 46 patients (62.2%) had sustained virologic suppression. Among the 28 patients who experienced VF, the median (IQR) duration of viremia during treatment with BIC/FTC/TAF was 19 (8–30) months; 16/28 patients (57.1%) who experienced VF achieved HIV-1 RNA < 50 c/mL by last visit with multifaceted interventions to improve adherence without changes to ART. Patients with VF, compared with those with sustained virologic suppression, were more likely to have M184V/I mutations at baseline (35.7% vs 12.2%, respectively; $P=0.04$), a lower CD4 cell count ($P=0.03$), and longer follow-up duration during treatment with BIC/FTC/TAF (43 vs 36 months; $P=0.047$). Emergence of an NRTI RAM (T69D/N) occurred in 1 patient who had experienced continuous viremia for 47 months.

Two patients discontinued BIC/FTC/TAF treatment during follow-up: 1 patient experienced a suspected AE of gastrointestinal and psychiatric nature that resulted in discontinuation, and 1 patient switched to a different ART regimen.

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ART=antiretroviral therapy
ARV=antiretroviral
AUC_T=area under the curve over dosing interval
BIC=bictegravir
c/mL=copies/mL
C_T=trough concentration
CD4=cluster of differentiation 4
CDC=Centers for Disease Control
C_{max}=maximum concentration
CV=coefficient of variation
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
eGFR_{Schwartz}=eGFR by Schwartz formula

FTC=emtricitabine
GLSM=geometric least squares mean
INSTI=integrase strand transfer inhibitor
INSTI-R=integrase strand transfer inhibitor resistance
iPK=intensive PK monitoring
M=E=missing=excluded
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
NRTI-R=nucleos(t)ide reverse transcriptase inhibitor resistance
PI=protease inhibitor
PK=pharmacokinetic(s)
PWH=people with HIV
Q=quartile
RAM=resistance-associated mutation

SAE=serious adverse event
STR=single-tablet regimen
TAF=tenofovir alafenamide
TAM=thymidine analog mutation
TC=total cholesterol
TEAE=treatment-emergent adverse event
TFV=tenofovir
TG=triglycerides
T_{max}=time to maximum concentration
TOS=tablet for oral suspension
TRAE=treatment-related adverse event
URTI=upper respiratory tract infection
VF=virologic failure
VS=virologically suppressed

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