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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.

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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 Labeling[1]

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 Study 1474, an ongoing phase 2/3 study, 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]

- Across Cohorts 1 to 3, BIC exposures in pediatric participants were generally consistent with those observed in adults, and FTC and TAF exposures were generally within known efficacy and safety ranges.[2,5] No PK data were presented for Cohort 4.
- In Cohorts 1 and 2, through Week 96, 5 Grade 3 or 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 (n=22), 18 participants 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]
- Through Week 240, virologic suppression was maintained in all 33 participants (100%) in Cohort 1, all 38 participants (100%) in Cohort 2, and in 17 of 18 participants (94.4%) in Cohort 3. BIC/FTC/TAF was well tolerated through 240 weeks of treatment, with no new safety concerns identified, and growth parameters remained consistent with expected age-related changes.[6]
- 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 Grade 1 TRAEs (15.1%) were observed, and; no serious or Grade 3 or 4 TRAEs were reported. One participant experienced a TEAE that led to treatment discontinuation.[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.[7,8]

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.[9,10]

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

In a retrospective cohort study of 117 ARV-naive adolescents, all patients achieved HIV-1 RNA <200 c/mL and 93 (85.3%) achieved HIV-1 RNA <50 c/mL after 6 months of treatment with BIC/FTC/TAF. Median CD4 count increased from 233 to 424 cells/mcL, and 94 (89.5%) patients had a CD4 count ≥200 cells/mcL. Safety data were not reported.[11]

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.[12]

Product Labeling[1]

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

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 with HIV-1.[2,4]

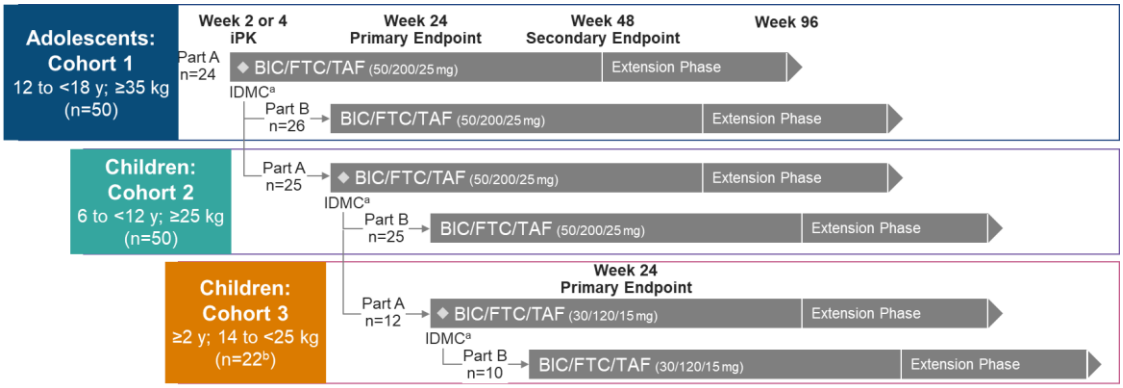
Cohorts 1 to 3[2]

VS adolescents aged 12 to <18 years (Cohort 1; n=50) and children aged 6 to <12 years (Cohort 2; n=50) received BIC/FTC/TAF 50/200/25 mg STR (Figure 1). Part A (Cohort 1, n=24; 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. In Cohort 3, children aged ≥2 years received BIC/FTC/TAF 30/120/15 mg STR (60% of full strength). All participants were switched from their 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/mcL, and $eGFR_{Schwartz}$ ≥90 mL/min/1.73 m^2.

Primary outcomes included assessment of BIC PK (AUC_T and C_T) at steady state at Weeks 2 and 4 (Cohorts 1 and 2) and safety and tolerability through Week 24. Secondary outcomes included the safety and tolerability of BIC/FTC/TAF through Week 48, the proportion of participants with virologic suppression (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 in CD4 counts at Weeks 24 and 48.

Figure 1. Study 1474 Cohorts 1 to 3: Study Design[2]



Abbreviation: IDMC=Independent Data Monitoring Committee.
[a]IDMC reviewed data once 50% of participants reached Week 12 and once all participants completed the iPK visit (Week 2 or 4).
[b]Six participants switched treatment to adult-strength BIC/FTC/TAF once they weighed >25 kg.

See Table 1 for baseline demographics and disease characteristics.[2,5]

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)/NR[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)

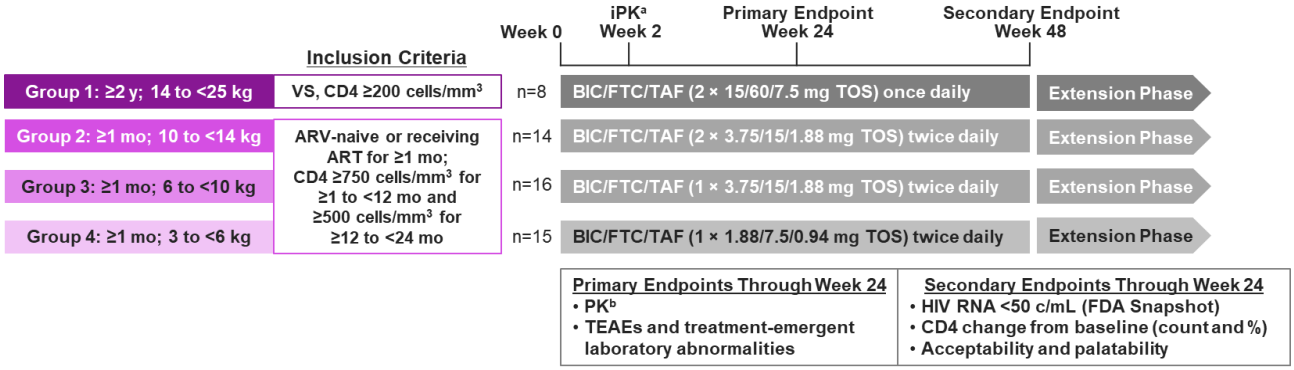
Abbreviation: NR=not reported.
[a]Median (IQR).
[b]1 participant had "other" race.

Cohort 4[4]

Cohort 4 consisted of children with HIV-1 aged ≥1 month to ≥2 years of age who weighed 3 kg to <25 kg TOS (Figure 2). 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 m^2 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-1 acquired via vertical transmission.

Figure 2. Study 1474 Cohort 4: Study Design[4]



[a]iPK assessments were performed for Groups 2 to 4.
[b]Data not presented.

See Table 2 for baseline demographics and disease characteristics.

Table 2. Study 1474 Cohort 4: Baseline Demographics and Disease Characteristics[4]

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)	1903 (1425, 3371)
	%	38.3 (31.7, 42.9)	33.6 (31.6, 35.7)	34.9 (27.6, 39.3)	33.8 (22.5, 34.9)
eGFR, median (Q1, Q3), mL/min/1.73 m^2		173 (150, 179)	151 (136, 158)	127 (110, 166)	109 (97, 111)

Abbreviation: Q=quartile.
[a]Countries of origin were as follows: South Africa, n=5; Uganda, n=2; and US, n=1.
[b]Countries of origin were as follows: Uganda, n=12 and South Africa, n=2.
[c]Countries of origin were as follows: Uganda, n=10; South Africa, n=4; and US, n=2.
[d]Countries of origin were as follows: Uganda, n=14 and South Africa, n=1.

PK results

Across Cohorts 1 to 3, BIC exposures in pediatric participants were generally consistent with those observed in adults in phase 3 clinical trials (Table 3). Although BIC C_T was 35% and 11% lower in adolescents and children, respectively, than what was observed in adults in phase 3 clinical trials, BIC exposures remained within predefined PK boundaries or above the protein-adjusted 95% effective concentration against wild-type HIV-1 virus. FTC and TAF exposures were generally similar to those observed in adults in phase 3 clinical trials within known efficacy and safety ranges of historical data in adults and children.[2,5] No PK data were presented for Cohort 4.[4]

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Table 3. Study 1474 Cohorts 1 to 3: Summary of PK Parameters[2,5]

PK Parameter		Cohort 1: Adolescents <12 to 18 Years	Cohort 2: Children 6 to <12 Years	BIC/FTC/TAF-Treated Adults[a]	Adolescent/ Adult GLSM[b] (90% CI)	Children/ Adult GLSM[b] (90% CI)	Cohort 3: ≥2 Years	BIC/FTC/TAF-Treated Adults[a]	Children/ Adult GLSM Ratio[b,c] (90% CI)
BIC[d]	n	50	50	1193	-	-	12	1193	-
	AUC_{τ}, h·ng/mL	89,100 (31)	128,000 (27.8)	102,000 (26.9)	86.3 (80–93)	125 (117–134)	105,892	98,430	107.6 (96.7–119.7)
	C_{max}, ng/mL	6240 (27.1)	9460 (24.3)	6150 (22.9)	100 (93.8–107)	153 (143–163)	9856.7	5986.1	164.7 (149.5–181.4)
	C_{τ}, ng/mL	1780 (44.4)	2360 (39)	2610 (35.2)	65.4 (58.3–73.3)	88.9 (80.6–98)	1604.8[e]	2453	65.4 (49.1–87.2)
FTC[f]	n	24	25	77	-	-	12	77	-
	AUC_{τ}, h·ng/mL	13,600 (21.7)	17,600 (36.9)	12,300 (29.2)	113 (102–124)	143 (127–159)	14,708.4	11,789.5	124.8 (111.8–139.2)
	C_{max}, ng/mL	2690 (34)	3890 (31)	2130 (34.7)	127 (111–145)	185 (162–210)	3629.6	2004	181.1 (150.1–218.5)
	C_{τ}, ng/mL	64.4 (25)	227 (322.8)[g]	96 (37.4)[h]	69.3 (61.6–77.9)	95 (69.9–129)	74.3[e]	89.9[h]	82.6 (47.7–143.1)
TAF[d]	n	49	47	486	-	-	12	77	-
	AUC_{τ}, h·ng/mL	196 (50.3)	278 (40.3)	142 (17.3)	128 (116–141)	183 (165–202)	281.7	194.6	144.7 (114.9–182.2)
	C_{max}, ng/mL	133 (70.2)	205 (44.6)	121 (15.4)	88.6 (75–105)	153 (136–173)	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; CV=coefficient of variations; GLSM=geometric least squares mean.
[a]Pooled population PK data from four phase 3 studies in adult PWH as reference data.
[b]Reported as ratio of test to reference.
[c]PK equivalence was met if the 90% CIs of the GLSM ratio were within the predefined equivalence boundary of 50 to 200%.
[d]Cohort 1 (adolescent) and Cohort 2 (children) data were obtained from population PK data.
[e]One participant had missing BIC and FTC PK data for C_{τ}.
[f]Cohort 1 (adolescent) and Cohort 2 (children) data were obtained from the iPK substudy (Part A).
[g]n=24.
[h]n=74.
Note: PK data presented for Cohorts 1 and 2 are means (CVs), and data for Cohort 3 are GLSMs.

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Efficacy and safety results

Cohorts 1 and 2: pooled efficacy results through Week 96

In an M=E analysis, high rates of virologic suppression (HIV-1 RNA <50 c/mL) were maintained through Week 96, with 100% (98/98) at Week 4, 100% (100/100) at Week 24, 99% (98/99) at Week 48, and 99% (95/96) at Week 96. Two participants met the criteria for resistance testing at Week 48, and no emergent resistance was detected. Three participants had a resistance mutation to FTC at baseline and maintained virologic suppression through Week 48. Overall, no treatment-emergent resistance was detected through Week 96. The mean changes from baseline in CD4 count between Weeks 2 and 48 ranged from -40 to +56 cells/mcL.[2]

Cohorts 1 and 2: pooled safety and tolerability results through Week 96

See Table 4 for safety outcomes in Cohorts 1 and 2 at Week 96.[3]

Table 4. Study 1474 Cohorts 1 and 2: Safety Outcomes at Week 96[2,3]

		Cohorts 1 and 2 (n=100)
Exposure to study drug, median (IQR), weeks		151.4 (125.6–153.5)
Any AEs, n (%)		86 (86)
Any-grade AEs in ≥10% of 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,[a] n (%)		13 (13)
Grade 3 or 4 AEs, n (%)		5 (5)
SAEs, n (%)		5 (5)
AEs that led to study drug discontinuation,[b] n (%)		1 (1)
Deaths, n		0

[a]AEs that were deemed study drug-related by investigators and occurred in >1 participant included abdominal discomfort (n=3) and transient neutropenia (n=2).
[b]Discontinuation due to Grade 2 insomnia and anxiety in Cohort 2. The participant who discontinued treatment in Cohort 2 was a 7-year-old female participant with a past medical history of anxiety and neuropsychiatric changes who experienced Grade 2 insomnia and anxiety at Week 20; this was considered treatment-related by the investigator.

Thirty participants experienced treatment-emergent Grade 3 or 4 laboratory abnormalities; the most frequent was hematuria (16%). Between Weeks 1 and 96, the median change in $eGFR_{Schwartz}$ was -15.5 mL/min/1.73 m^2.[3] From baseline to Week 48, slight changes in height and weight Z-scores were observed (Table 5).[2]

Table 5. Study 1474 Cohorts 1 and 2: Changes From Baseline in Height and Weight Z-Scores[13a]

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)

Median (IQR)			Cohort 1: Adolescents (n=50)	Cohort 2: Children (n=50)	Cohorts 1 and 2 (n=100)
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)

[a]Z-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 96[5]

Through Week 96, virologic suppression was maintained in all participants in an M=E analysis: Weeks 24 (20/20), 48 (21/21), and 96 (17/17). By FDA Snapshot analysis, virologic suppression was achieved in 91% (20/22) and 95% (21/22) of participants at Weeks 24 and 48, respectively. The median CD4 change from baseline was -137 cells/mcL.

Cohort 3: safety and tolerability results through Week 48[5]

As of data cutoff, 11 participants who switched to full-dose BIC/FTC/TAF after reaching a weight of ≥25 kg were included in the safety analyses. Of the 22 participants included in this analysis, none experienced any Grade 3 to 4 AEs or SAEs, and no participants discontinued the study drug due to an AE.

Table 6. Study 1474 Cohort 3: Safety Outcomes at Week 48[5]

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 ≥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]

[a]Neutropenia (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.
[b]The 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 m^2. 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.[14]

Through Week 48, ≥79% of participants who swallowed the tablets whole reported them as "easy" or "super easy" to swallow, and ≥91% of participants described the tablets as neutral or positive at palatability assessments. Median adherence by pill count was 99%.[5]

Cohorts 1 to 3: efficacy results through Week 240[6]

Virologic suppression was maintained through Week 240 in all 33 participants (100%) in Cohort 1, all 38 participants (100%) in Cohort 2, and in 17 of 18 participants (94.4%) in Cohort 3. Throughout the study period, absolute CD4 cell count and CD4 percentage remained stable across all cohorts.

Cohorts 1 to 3: safety results through Week 240[6]

BIC/FTC/TAF was well tolerated throughout Week 240, with no new safety concerns identified.

Table 7. Study 1474 Cohorts 1 to 3: Safety Outcomes Through Week 240[6]

Safety Outcome	Cohort 1: Adolescents (n=50)	Cohort 2: Children 6 to <12 Years (n=50)	Cohort 3: Children ≥2 Years (n=22)
Study drug exposure duration, median, weeks	392	371	279
Any AE, n (%)	45 (90)	47 (94)	21 (95)
Grade ≥3	11 (22)	6 (12)	3 (14)
SAEs	8 (16)	5 (10)	0
TRAEs, n (%)	5 (10)	10 (20)	3 (14)
Grade ≥3	1 (2)[a]	0	0
Serious TRAE	1 (2)[a]	0	0
AEs that led to treatment discontinuation, n (%)	1 (2)[b]	2 (4)[c]	0

[a]Grade 3 AE of upper abdominal pain, nausea, and vomiting occurred in 1 participant on Day 1957. BIC/FTC/TAF was temporarily interrupted and resumed 5 days later.
[b]Treatment was discontinued due to pulmonary tuberculosis.
[c]One participant discontinued due to pulmonary tuberculosis, and 1 participant discontinued due to drug-related insomnia and worsening anxiety.

Growth parameters remained consistent with expected age-related changes through Week 240 (Table 8).

Table 8. Study 1474 Cohorts 1 to 3: Baseline and Week 240 Height, Weight, and BMI Z-Scores[6a]

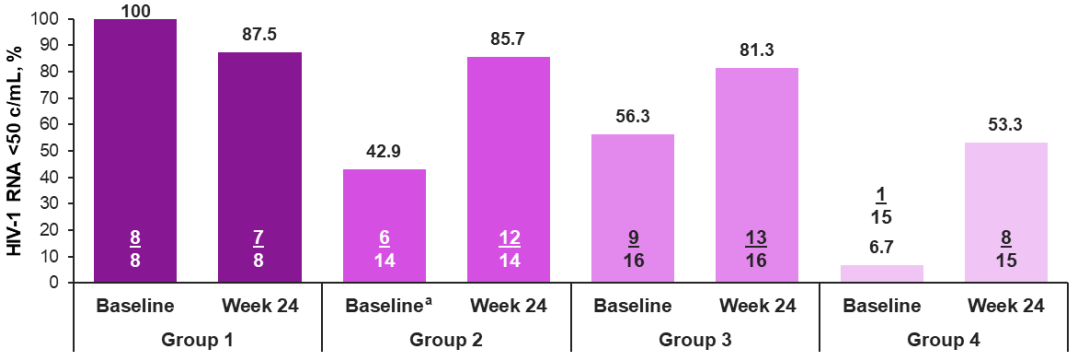
Z-Score, Median		Cohort 1: Adolescents (n=50)	Cohort 2: Children 6 to <12 Years (n=50)	Cohort 3: Children ≥2 Years (n=22)
Height	Baseline	-0.87	-0.67	-0.53
	Week 240	-0.77	-0.57	-0.14
Weight	Baseline	-0.54	-0.35	-0.35
	Week 240	-1.03	0.11	-0.4
BMI	Baseline	-0.1	0.08	-0.11
	Week 240	-0.66	0.36	0.11

[a]Z-scores were generated based on US CDC Growth Charts growth charts from year 2000.

Cohort 4: efficacy results through Week 24[4]

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 3.

Figure 3. Study 1474 Cohort 4: Virologic Suppression (HIV-1 RNA <50 c/mL) at Baseline and Week 24 (FDA Snapshot)[4]



[a]Baseline 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 24[4]

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 or 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 24[4]

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.
[a]Vomiting and ALT increased and amylase increased (each, n=1).
[b]Vomiting and pruritus (each, n=1).
[c]Vomiting (n=4).
[d]Pulmonary tuberculosis; unrelated to BIC/FTC/TAF.
[e]Pneumonia; unrelated to BIC/FTC/TAF.
[f]Occurred 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 4: Baseline and Week 24 Height/Length and Weight Z-Scores[a] and eGFR[4]

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

[a]Z-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.

At Week 24, 42.9% of the 49 caregivers of study participants with available data reported a rating of “super good” and 46.9% reported “good” palatability. Of the 51 caregivers with available data, 98% reported that the entire dose was successfully administered to the participants.

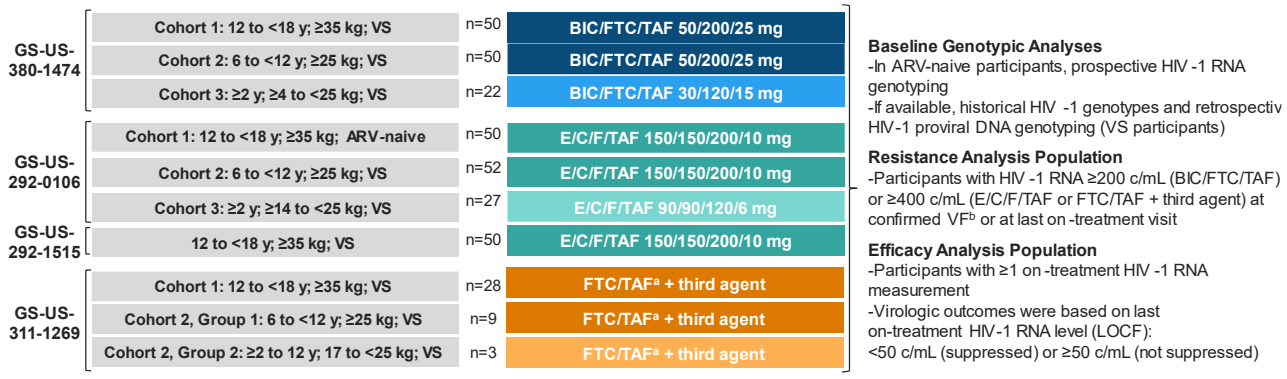
Pooled Analysis of Resistance to FTC/TAF-Based Regimens in Pediatric Studies

Study design and demographics[7]

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 4). 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 4. Pooled Analysis of Resistance: Study Design[7]



Abbreviation: LOCF=last observation carried forward.

[a]In 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.

[b]Confirmed 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/TAF[7]

Baseline resistance

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

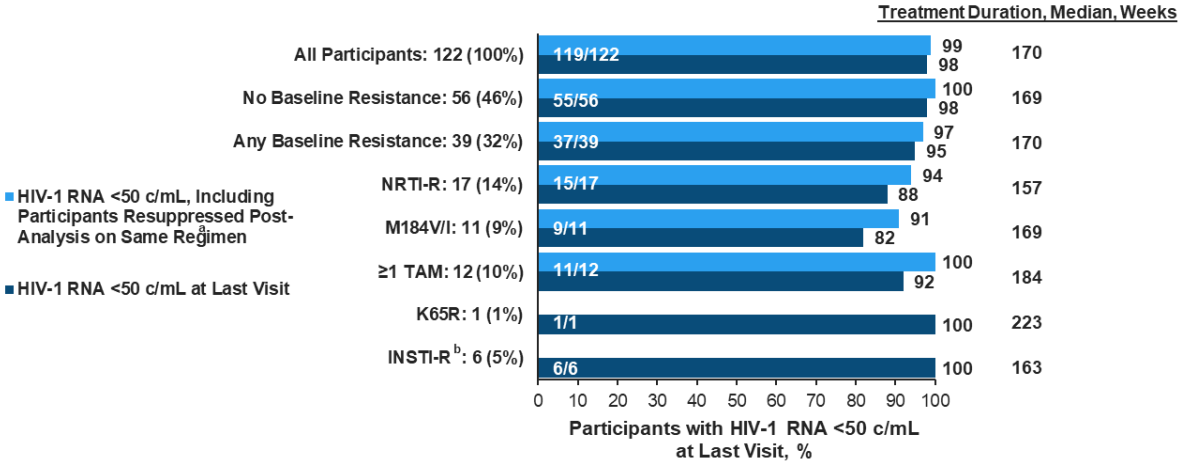
Table 11. Pooled Analysis of Resistance: Baseline Resistance Data in BIC/FTC/TAF-Treated, VS Participants[7,8]

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.
[a]Those without integrase resistance data were considered as having no INSTI RAM.
[b]This participant maintained virologic 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 5.

Figure 5. Pooled Analysis of Resistance: Virologic Suppression Among BIC/FTC/TAF-Treated Participants at Last Visit by Baseline Resistance[7]



[a]This 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.
[b]INSTI-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 demographics[9]

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%.[9,10]

From baseline to Week 48, percentages of participants who were underweight decreased, percentages of those with normal weight increased and percentages of those who were overweight or obese remained stable (Table 12). 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.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).[10]

Table 12. Change From Baseline to Week 48 in Weight and Acceptable Lipid Parameters in Participants Who Switched to BIC/FTC/TAF[10]

Parameter, %		BIC/FTC/TAF (n=21)	
		Baseline	Week 48
BMI	Underweight	13.6	9.1
	Normal weight	63.6	68.2
	Overweight or obese	22.7	22.7
Participants with acceptable lipid levels	TC	42.9	85.7
	LDL	47.6	76.2
	HDL	76.2	52.4
	TG	47.6	76.2

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

Retrospective Cohort Study in Mexico[11]

A retrospective cohort study in Mexico described baseline characteristics and 6-month outcomes for 117 ARV-naive adolescents aged 15 to 19 years who initiated BIC/FTC/TAF between 2019 and 2025.

At baseline, the median (IQR) age was 19 (18–19) years, and 113 patients (96.6%) were male. Sixty-six patients (56.4%) had HIV-1 RNA <100,000 c/mL, 32 (27.4%) had a viral load of 100,000 to 500,000 c/mL and 19 (16.2%) had a viral load of >500,000 c/mL. Forty-four patients (37.6%) had a CD4 count <200 cells/mcL.

At 6 months, 100% of patients achieved HIV-1 RNA <200 c/mL, 93 patients (85.3%) had HIV-1 RNA<50 c/mL, and 94% of patients remained on treatment with BIC/FTC/TAF. The median CD4 count increased from 233 cells/mcL at baseline to 424 cells/mcL at 6 months, and 94 (89.5%) had a CD4 count ≥200 cells/mcL.

Safety data were not reported.

Retrospective, Single-Center Study in France[12]

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.

Compared with those with sustained virologic suppression, patients with VF 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 a longer follow-up duration during treatment with BIC/FTC/TAF (43 vs 36 months; *P*=0.047). One patient developed an NRTI RAM (T69D/N) after 47 months of continuous viremia.

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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2 Years Weighing 14 to < 25 kg [Presentation]. Paper presented at: International Workshop on HIV & Pediatrics; 27-28 July, 2022; Montreal, Quebec, Canada.

Abbreviations

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