Bictegravir/Emtricitabine/Tenofovir Alafenamide Low-Dose Tablet Relative Bioavailability in Healthy Volunteers and PK in Children With HIV

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Sophia R. Majeed, Polina German, Steve K. West, Shaolan (Shirley) Xiang, P.J. Costales, Deqing Xiao, Michael Keeney, Joanna Koziara, Jenna Scott, Hiba Graham, Cheryl Pikora, Anita Mathias — Gilead Sciences, Inc., Foster City, CA

Introduction

- Few antiretroviral options exist for very young children living with HIV and no single-tablet regimen (STR) is used or approved for this population
- Bictegravir (BIC; B) is a novel, unboosted integrase strand transfer inhibitor (INSTI), with a high genetic barrier to resistance and low potential for drug-drug interactions, approved for use in children weighing ≥25 kg living with HIV[1-3]
- BIC has been coformulated with emtricitabine (FTC; F) and tenofovir alafenamide (TAF) into a once-daily STR (B/F/TAF) in a reduced strength for children weighing 14–<25 kg
  - Reformulated reduced strength is B/F/TAF 30/120/15 mg (60% of adult strength STR)

Objectives

Phase 1 Study

- **Primary:**
  - To evaluate the relative bioavailability of the reformulated B/F/TAF low-dose STR (30/120/15 mg) vs the full-strength STR (50/200/25 mg)
  - To evaluate the effect of food on the pharmacokinetics (PK) of the B/F/TAF low-dose STR
- **Secondary:**
  - To evaluate the safety and tolerability of single doses of the B/F/TAF low-dose STR

Phase 2/3 Part A Study (NCT02881320)

- **Primary:**
  - To confirm the dose of the B/F/TAF low-dose STR in virologically suppressed children with HIV aged ≥2 y and weighing 14–<25 kg
- **Secondary:**
  - To evaluate the safety and tolerability of the B/F/TAF low-dose STR through Week 24 in virologically suppressed children with HIV aged ≥2 y and weighing 14–<25 kg

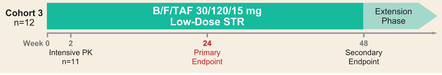
Methods

Phase 1 Study Design

Treatment Sequence	Period 1		Period 2		Period 3	
	Day 1	Days 2–8	Day 9	Days 10–16	Day 17	Day 21
ABC: n=9	A	Washout	B	Washout	C	Discharge
ACB: n=9	A	Washout	C	Washout	B	Discharge
BCA: n=9	B	Washout	C	Washout	A	Discharge
BAC: n=9	B	Washout	A	Washout	C	Discharge
CBA: n=9	C	Washout	B	Washout	A	Discharge
CAB: n=9	C	Washout	A	Washout	B	Discharge

- Randomized, open-label, single-center, single-dose, 3-period, crossover study in healthy normal subjects (N=54; 48 evaluable)
  - **Treatment A:** single-dose, B/F/TAF 50/200/25-mg, full-strength STR, **fasted** conditions
  - **Treatment B:** single-dose, B/F/TAF 30/120/15-mg, low-dose STR, **fasted** conditions
  - **Treatment C:** single-dose, B/F/TAF 30/120/15-mg, low-dose STR, **fed** (~1000 kcal and ~50% fat) conditions
- Key inclusion criteria:
  - Healthy male and female participants aged 18–≤45 y
  - Body mass index 19.0–≤30.0 kg/m² at screening
  - Creatinine clearance (using Cockcroft-Gault method) ≥90 mL/min

Phase 2/3 Part A Study Design



- Key inclusion criteria:
  - Aged 2–<18 y and body weight 14–<25 kg (31–<55 lb)
  - Estimated glomerular filtration rate (eGFR; Schwartz formula) ≥90 mL/min/1.73 m²
  - Plasma HIV-1 RNA <50 copies/mL for ≥6 mo
  - Cluster of differentiation-4 (CD4) count ≥200 cells/µL
  - No documented or suspected resistance to FTC, tenofovir (TFV), or INSTIs, including, but not limited to, reverse transcriptase resistance mutations K65R and M184V/I

PK Analyses

- Intensive PK samples were collected over:
  - 96 h postdose on Days 1, 9, and 17 in the Phase 1 Study
  - 24 h postdose on Week 2 in the Phase 2/3 Part A Study
- PK parameters of BIC, FTC, and TAF were estimated by noncompartmental analysis using Phoenix® WinNonlin® 6.3/6.4 (Certara USA, Inc., Princeton, NJ)
  - **Phase 1:** area under concentration-time curve from time 0 to infinity (AUC_{inf}), AUC from time 0 to time of last measurable concentration (AUC_{last}), and maximal concentration (C_{max})
  - **Phase 2/3 Part A:** AUC over dosing interval (AUC_{tau}), C_{max}, and trough concentration at end of dosing interval (C_{tau})

Safety Analyses

- Adverse event (AE) monitoring and clinical laboratory abnormalities

Statistical Analyses

- PK parameters were compared between test and reference treatments using geometric least-squares mean (GLSM) ratios and 90% confidence intervals (CIs), with predefined PK equivalence boundary of 70–143% (Phase 1) and 50–200% for BIC (Phase 2/3)
  - **Phase 1:** test (low-dose STR fasted) vs reference (full-strength STR fasted), and test (low-dose STR fed) vs reference (low-dose STR fasted)
  - **Phase 2/3 Part A:** test (virologically suppressed children with HIV aged ≥2 y and weighing 14–<25 kg) vs reference (B/F/TAF-treated adults with HIV; historical data)

Results

Phase 1: Comparison of PK Parameters Between B/F/TAF Low-Dose and Full-Strength STRs

Analyte	PK Parameter Geometric Mean	B/F/TAF 30/120/15 mg Low-Dose STR, Fasted n=52*	B/F/TAF 50/200/25 mg Full-Strength STR, Fasted n=53	B/F/TAF Low-Dose vs Full-Strength STR, Dose-Normalized %GLSM Ratio (90% CI) n=53†
BIC	AUC_{inf}, h·ng/mL	132,000	118,000	112 (106, 117)
	AUC_{last}, h·ng/mL	128,000	115,000	111 (106, 117)
	C_{max}, ng/mL	6890	5870	117 (112, 123)
FTC	AUC_{inf}, h·ng/mL	9890	9780	101 (99.1, 103)
	AUC_{last}, h·ng/mL	9530	9530	100 (97.7,102)
	C_{max}, ng/mL	2030	1960	104 (98.2, 109)
TAF	AUC_{inf}, h·ng/mL	207	229‡	90.5 (84.7, 96.6)
	AUC_{last}, h·ng/mL	204	226	90.4 (84.1, 97.2)
	C_{max}, ng/mL	332	349	95.4 (83.0, 109)

*Dose normalization of test treatment was calculated by dividing each PK parameter value by ratio of test dose/reference dose (0.6); †Dose-normalized %GLSM ratio and 90% CI were calculated by dividing dose-normalized GLSM of PK parameter from test treatment by GLSM of PK parameter from reference treatment; ‡n=52.

- GLSM ratios and associated 90% CIs for PK parameters of BIC, FTC, and TAF were all within protocol-defined equivalence boundary of 70–143% (for dose-normalized comparisons)

Phase 1: Comparison of PK Parameters Following Single-Dose Administration of B/F/TAF Low-Dose STR in Fed vs Fasted Conditions

Analyte	PK Parameter Geometric Mean	B/F/TAF Low-Dose STR, Fed n=52	B/F/TAF Low-Dose STR, Fasted n=52	B/F/TAF Low-Dose STR, Fed vs Fasted %GLSM Ratio (90% CI) n=52
BIC	AUC_{inf}, h·ng/mL	82,100	79,100	104 (98.8, 109)
	AUC_{last}, h·ng/mL	80,000	77,100	104 (98.8, 109)
	C_{max}, ng/mL	4090	4140	98.8 (94.1, 104)
FTC	AUC_{inf}, h·ng/mL	5590	5940	94.2 (92.3, 96.2)
	AUC_{last}, h·ng/mL	5370	5720	94.0 (91.9, 96.2)
	C_{max}, ng/mL	1000	1220	82.3 (78.0, 86.8)
TAF	AUC_{inf}, h·ng/mL	176*	124	142 (131, 153)
	AUC_{last}, h·ng/mL	160	123	130 (121, 140)
	C_{max}, ng/mL	112	199	56.3 (49.0, 64.6)

*n=35.

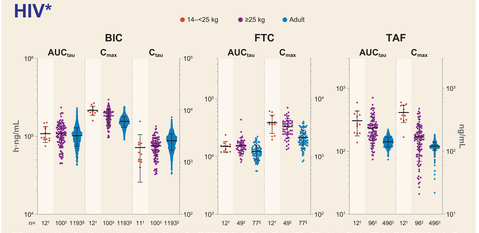
- GLSM ratios and 90% CIs for PK parameters were all within PK equivalence boundary of 70–143% after administration with a high-fat meal for both FTC and BIC
- Mean TAF AUC increased by 30–42% and C_{max} decreased by 44% after administration with a high-fat meal compared with fasted administration

Phase 2/3: Baseline Characteristics

		Children ≥2 y; 14–<25 kg n=12
Median age, y (range)		6 (3–9)
Median weight, kg (range)		20.1 (14.6–24.1)
Female, n (%)		7 (58)
Race, n (%)	Asian	5 (42)
	Black	7 (58)
Country, n (%)	South Africa	3 (25)
	Thailand	5 (42)
	USA	4 (33)
HIV-1 RNA <50 copies/mL, n (%)		12 (100)
Median CD4 cell count/µL (Q1, Q3)		841 (703, 1238)
Median eGFR, mL/min/1.73 m² (Q1, Q3)		151.0 (141.5, 167.0)
Vertical transmission, n (%)		12 (100)

Q, quartile.

Phase 2/3: B/F/TAF PK in Children and Adults With HIV*



*AUC_{tau}, units: h·ng/mL (left axes); C_{max} and C_{tau}, units: ng/mL (right axes). †Intensive PK analysis: Study GS-US-380-1474 (Cohort 3); ‡Population PK analysis (BIC and TAF) and intensive PK analysis (FTC): Study GS-US-380-1474 (Cohorts 1 and 2); §Population PK analysis (BIC) and intensive PK analysis (FTC): Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1478; ¶Population PK analysis (Studies GS-US-380-1489 and GS-US-380-1490).

Phase 2/3: Intensive BIC, FTC, and TAF PK Data

Analyte	PK Parameter Mean (%CV)	Children ≥2 y; 14–<25 kg n=12*	Adults n=1193†	Children/Adults GMR% (90% CI)
BIC	AUC_{tau}, h·ng/mL	109,000 (24)	102,000 (27)	109 (96.7, 122)
	C_{max}, ng/mL	10,100 (21)	6150 (23)	166 (149, 184)
	C_{tau}, ng/mL	2000 (78)‡	2610 (35)	67.7 (49.6, 92.4)
FTC	AUC_{tau}, h·ng/mL	14,900 (23)	12,300 (29)	124 (110, 139)
	C_{max}, ng/mL	3660 (34)	2130 (35)	173 (144, 209)
	C_{tau}, ng/mL	228 (235)‡	96 (37)§	89.0 (49.3, 161)
TAF	AUC_{tau}, h·ng/mL	305 (43)	229 (63)	145 (115, 182)
	C_{max}, ng/mL	414 (31)	277 (62)	173 (140, 214)

*1 participant excluded from BIC and FTC PK analyses due to noncompliance with study drug; †From pooled population PK data from 4 Phase 3 studies in adults with HIV on B/F/TAF; ‡n=77 for FTC and TAF PK analyses; §n=10; ¶n=74. GMR, geometric mean ratio.

- BIC AUC_{tau} and C_{max} were within prespecified 50–200% lack of PK alteration boundary
- BIC C_{tau} was 32% lower in children vs adults
  - Mean BIC C_{tau} was ~12-fold above the protein-adjusted 95% effective concentration for wild-type virus (162 ng/mL)
  - Not considered to be clinically meaningful due to high rate of virologic suppression in children[4]
- FTC and TAF exposures in children and adults were comparable

Safety

- Phase 1: all AEs were Grade 1 (mild) in severity
  - AEs considered related to study drug were reported in 6 participants (11%) after receiving B/F/TAF full-strength STR under fasted conditions, 3 (6%) after receiving B/F/TAF low-dose STR under fasted conditions, and 3 (6%) after receiving B/F/TAF low-dose STR under fed conditions
  - No deaths, serious AEs, or AEs leading to study drug discontinuations
  - Most laboratory abnormalities were Grade 1 or 2 (mild or moderate) in severity
- Phase 2/3: all AEs were Grade 1 or 2 in severity
  - 3 participants (25%) had AEs related to study drug
  - No deaths, serious AEs, or AEs leading to study drug discontinuations
  - 2 participants had Grade 3 or 4 laboratory abnormalities: 1 with Grade 3 decreased neutrophils at Week 24 and 1 with Grade 4 decreased neutrophils at Week 1 (Grade 3 decreased neutrophils at baseline)

Conclusions

Phase 1 Study

- Single doses of the B/F/TAF full-strength and low-dose STRs were generally well tolerated
- GLSM ratios and 90% CIs for dose-normalized comparisons of BIC, FTC, and TAF PK parameters between the full-strength and low-dose B/F/TAF STRs were within PK equivalence boundary of 70–143%
- Administration of the B/F/TAF low-dose STR with a high-fat meal had no clinically relevant food effect
- These data support the use of the B/F/TAF low-dose STR without regard to food

Phase 2/3 Part A Study

- B/F/TAF was well-tolerated in children aged ≥2 y and weighing 14–<25 kg
- Exposures of BIC, FTC, and TAF in children were within the range of exposures observed in adults and pediatric patients weighing ≥25 kg treated with B/F/TAF

Collectively, these data support evaluation of the B/F/TAF low-dose STR for the treatment of HIV-1 infection in children aged ≥2 y and weighing 14–<25 kg

For information on the safety and efficacy of the B/F/TAF low-dose STR, see Rodriguez CA, et al, CROI 2020, poster 3929

References: 1. Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc; 6/19; 2. Gallant JE, et al. J Acquir Immune Defic Syndr 2017;75:61-6; 3. Tsiang M, et al. Antimicrob Agents Chemother 2016;60:7086-97; 4. Rodriguez C, et al. CROI 2020, poster 3929.
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