Bictegravir/FTC/TAF Single-Tablet Regimen in Adolescents and Children: Week 48 Results

Video Link

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Introduction

- Bictegravir (BIC; B) is a novel, unboosted integrase strand transfer inhibitor (INSTI)[1-3]
  - Low DDI potential
  - Co-formulated with emtricitabine (FTC; F) and tenofovir alafenamide (TAF) as a small, single-tablet regimen given once daily without regard to food
- The single-tablet regimen, bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), is currently approved for adults living with HIV based on results of five Phase 3 studies showing:[4-8]
  - High rates of viral suppression
  - No treatment-emergent resistance
- B/F/TAF has been shown to be well-tolerated in children, adolescents and adults
  - TAF–based regimens show improved bone and renal safety compared with tenofovir disoproxil fumarate (TDF)–based regimens[9,10]
  - We have previously demonstrated pharmacokinetics (PK), safety, and efficacy of B/F/TAF in adolescents and children to be similar to that for adults through 24 weeks[11,12]
- We now report 48 weeks of PK, safety, and efficacy of B/F/TAF in virologically suppressed adolescents and children from Study 380-1474

Study Objectives

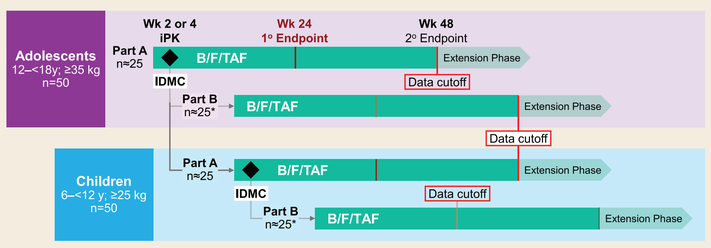
- **Primary:** to determine the plasma PK of BIC, and evaluate the safety and tolerability of the adult-strength tablet of B/F/TAF through 24 weeks of treatment in adolescents and children living with HIV-1
- **Secondary:** to evaluate the safety and tolerability of the adult-strength tablet of B/F/TAF through 48 weeks, and its antiviral activity at 24 and 48 weeks in adolescents and children living with HIV-1

Methods

Study Design

Eligibility Criteria
- HIV-1 RNA <50 copies/mL for ≥6 mo
- CD4 count ≥200 cells/μL
- eGFR ≥90 mL/min/1.73 m² (Schwartz)

- Phase 2/3, open-label, multicenter, multi-cohort, single-arm study (NCT02881320)
  - Part A: Intensive PK was assessed to confirm the dose of B/F/TAF (50/200/25 mg QD)
  - Part B: Following dose confirmation and IDMC review of short-term safety from Part A, additional participants were enrolled to complete the cohort

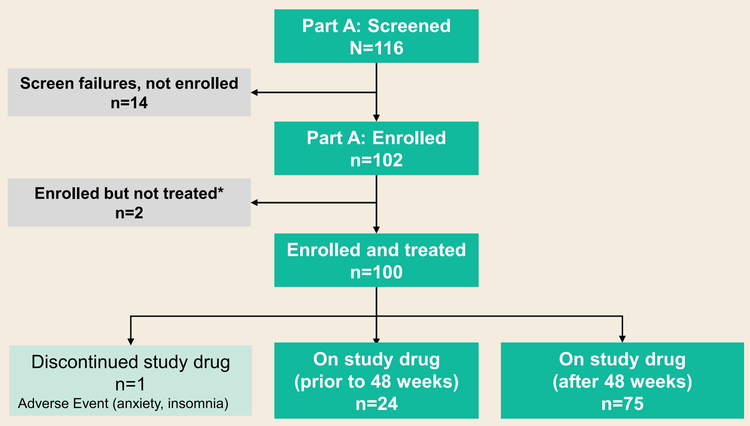


*Including participants from Part A; independent data monitoring committee (IDMC)—50% participants reach Wk 12 and all complete iPK (intensive PK) visit.
eGFR, estimated glomerular filtration rate.

Study Assessments

- PK: intensive and sparse PK samples collected to confirm steady-state exposure of BIC, FTC, and TAF
  - BIC PK parameters predicted from population PK modeling
- Safety: adverse events (AEs) and clinical laboratory abnormalities
- Efficacy: HIV-1 RNA and CD4 cell count
- Palatability and Acceptability:
  - Investigator (or designee) used age-appropriate questions to ascertain tablet palatability (taste) and acceptability (acceptable product shape and size) at Day 1 (baseline) and Day 28 (Week 4)
- Adherence: assessed by pill count at each visit

Disposition: Adolescents and Children



* Withdrew consent (n=1), Investigator discretion (n=1)

Results

Baseline Demographics

	Adolescents n=50	Children n=50
Median age, y (range)	15 (12–17)	10 (6–11)
Median weight, kg (Q1, Q3)	45 (40, 56)	29 (27, 33)
Female, n (%)	32 (64)	27 (54)
Race, n (%)		
Asian	13 (27)	11 (22)
Black	32 (65)	36 (72)
White	1 (2)	2 (4)
Other	3 (6)	1 (2)
Country, n (%)		
South Africa	16 (32)	24 (48)
Thailand	12 (24)	10 (20)
Uganda	6 (12)	8 (16)
US	11 (22)	13 (26)

Race excludes 1 participant with race "not permitted" in Cohort 1. Q, quartile.

Baseline Disease Characteristics

	Adolescents n=50	Children n=50
HIV-1 RNA <50 copies/mL, n (%)	50 (100)	50 (100)
Median CD4 cell count, /μL (Q1, Q3)	750 (586, 926)	898 (707, 1121)
Median eGFR, mL/min/1.73 m² (Q1, Q3)	145 (134, 170)	154 (144, 173)
Mode of transmission, n (%)		
Vertical	45 (90)	48 (96)
Unknown	4 (8)	1 (2)
Heterosexual sex	0	0
Transfusion	9 (1, 17)	1 (2)
Median time on ART, y (range)		8 (5, 11)
ARV regimen prior to enrollment, n (%)		
Multiple tablets	35 (70)	46 (92)
BID dosing	24 (48)	36 (72)

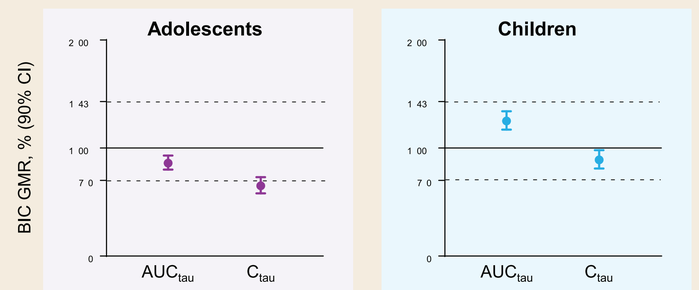
ARV, antiretroviral; BID, twice daily; SD, standard deviation.

ARV Treatment Prior to Switching to B/F/TAF

		Adolescents n=50	Children n=50
NRTI backbone, n (%)	AZT/3TC	18 (36)	27 (54)
	ABC/3TC	12 (24)	22 (44)
	TDF/FTC	4 (8)	1 (2)
	TAF/FTC	10 (20)	0
	Other NRTI	6 (12)	0
Third agents, n (%)	PI	17 (34)	26 (52)
	NNRTI	21 (42)	21 (42)
	INSTI	13 (26)	3 (6)
STRs, n (%)	ABC/3TC/DTG	2 (4)	0
	EVG/COBI/FTC/TAF	8 (16)	0
	RPV/FTC/TAF	1 (2)	0
	AZT/3TC/NVP	4 (8)	4 (8)

3TC, lamivudine; ABC, abacavir; AZT, atazanavir; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RPV, rilpivirine; STR, single tablet regimen; ZDV, zidovudine.

Population Pharmacokinetics: Adolescents and Children



- BIC AUC_{tau} was similar in adolescents and children relative to adults
- BIC C_{tau}:
  - Lower in adolescents compared with adults but remains >11-fold above the $paEC_{50}$
  - Similar in children relative to adults
- Exposures of FTC* and TAF† were within the range of historical data with adults and pediatrics treated with Elvitegravir/Cobicistat/F/TAF

*Estimated using non-compartmental analysis; †Estimated using population PK analysis.
AUC_{tau}, area under curve over dosing interval; Cmax, maximum concentration; C_{tau}, trough concentration; GMR, geometric mean ratio (adults=reference); $paEC_{50}$, protein-adjusted 50% effective concentration.

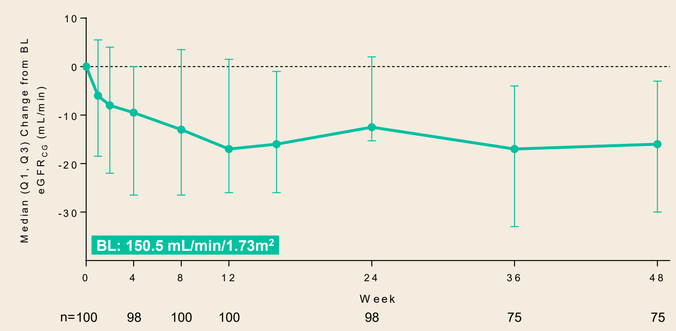
Overall Safety

Participants, n (%)	6–<18 y n=100
Any grade AE	69 (69)
Any grade AE in ≥5%	
Upper respiratory tract infection	19 (19)
Diarrhea	9 (9)
Cough	7 (7)
Headache	6 (6)
Nasopharyngitis	6 (6)
Viral upper respiratory tract infection	5 (5)
Grade 3/4 AE	1 (1)
AE related to study drug*	10 (10)
Serious AE†	2 (2)
AE leading to study drug discontinuation‡	1 (1)
Death	0

*The most comment AE related to study drug was abdominal discomfort (n=2); all other related AEs occurred in 1 participant each.
†Serious AEs: Grade 2, unrelated abdominal pain (n=1), Grade 2, unrelated lung abscess (n=1).
‡Grade 2 insomnia and anxiety.

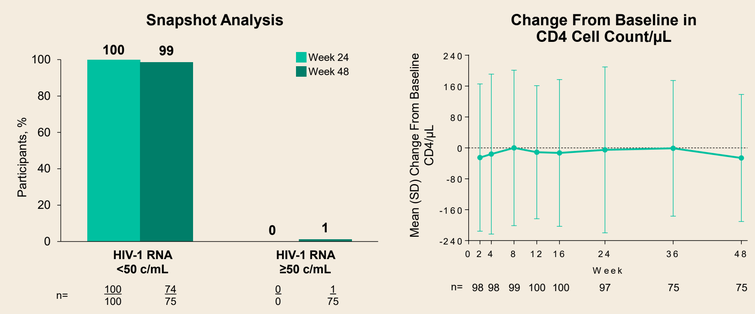
- Most common Grade 3/4 laboratory abnormality was hematuria (n=11 [11%])
  - 10 of these participants were adolescent females, had normal menses, and remained on study drug
  - No other Grade 3/4 laboratory abnormality was reported in ≥5% of participants

Estimated Glomerular Filtration Rate (Schwartz)



- Median changes in eGFR ranged from -6.0 to -17.0 mL/min/1.73 m² between Weeks 1 and 48
- Changes in eGFR in adolescents and children were:
  - Consistent with the known renal creatinine transporter effect of BIC[13, 14]
  - Not considered clinically significant

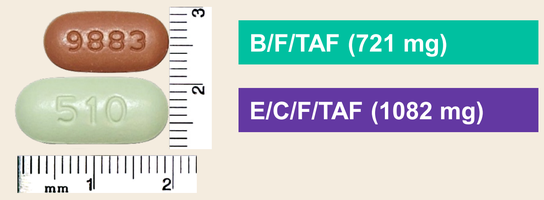
Efficacy: Virologic Outcomes



- No participant developed resistance to the components of B/F/TAF

Adherence and Participant-Reported Palatability & Acceptability

- All 100 participants reported B/F/TAF as palatable, and with acceptable shape and size (15 mm x 8 mm)
- Median (Q1, Q3) adherence rate
  - Up to Week 24 (n=100): 98.8% (98.0, 100.0)
  - Up to Week 48 (n=75): 98.8% (96.4, 99.5)



*Comparative tablet sizes of B/F/TAF and E/C/F/TAF approved for adolescent use (E/C/F/TAF also approved for use in children 6 to <12 years and > 25 kg); numbers in parentheses are total weights in mg of tablets.
[Note: tablet size is not intended to compare clinical efficacy and safety, indications, dosing regimens, or treatment adherence.]

Conclusions

- In adolescents and children (aged 6 to <18 years, ≥25 kg) living with HIV-1 infection:
  - Exposures of BIC, FTC, and TAF with adult-strength B/F/TAF were within the ranges of exposures observed in adults in Phase 3 trials of B/F/TAF
  - B/F/TAF demonstrated high rates of virologic suppression with no development of resistance to the components
  - B/F/TAF was well tolerated, found to be palatable, with high adherence, and had only one discontinuation due to an AE
  - Further investigations of B/F/TAF with age-appropriate (low-dose) formulations in younger children are ongoing

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