Bictegravir/FTC/TAF Single-Tablet Regimen in Adolescents: Week-24 Results

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Introduction

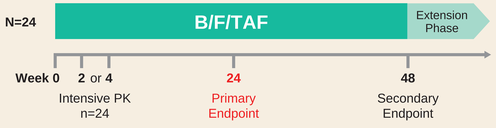
- In 2015, ~20% of all new HIV infections in the USA occurred in youth aged 13–24 years[1]
- Adherence to antiretroviral therapy can be challenging for adolescents, and the resulting poor adherence can increase their risk of drug resistance and virologic failure[2-4]
- Bictegravir (BIC [B]) is a novel, unboosted integrase strand transfer inhibitor (INSTI), with a high genetic barrier to resistance and low potential for drug-drug interactions[5,6]
- BIC has been coformulated with emtricitabine (FTC [F]) and tenofovir alafenamide (TAF) into a once-daily, single-tablet regimen (B/F/TAF) of small tablet size, which can be taken without regard to food
- This is the 1st study to report the pharmacokinetics (PK), safety, and efficacy of B/F/TAF in a pediatric population

Objectives

- **Primary:** to determine the plasma PK of BIC, and evaluate the safety and tolerability of B/F/TAF through 24 wk of treatment in HIV-1–infected adolescents
- **Secondary:** to evaluate the safety and tolerability of B/F/TAF through 48 wk, and its antiviral activity at 24 and 48 wk in HIV-1–infected adolescents

Methods

Study Design



- Phase 2/3, open-label, multicenter, multicohort, single-arm study in HIV-1–infected, virologically suppressed adolescents (NCT02881320)
- Key inclusion criteria:
  - Aged 12–<18 y; weight ≥35 kg
  - HIV-1 RNA <50 copies/mL for ≥6 mo
  - CD4 count ≥200 cells/μL
  - Estimated glomerular filtration rate (eGFR; Schwartz formula) ≥90 mL/min/1.73 m^2
- Safety assessments: adverse events (AEs) and clinical laboratory abnormalities
- Efficacy assessments: HIV-1 RNA viral load and CD4 cell count
- PK assessment: steady-state plasma PK parameters calculated for BIC, FTC, and TAF

Results

Disposition

- Screened: N=25
- Enrolled: N=24
- No study drug discontinuations (D/C) through Week 24
- Median (quartile [Q] 1, Q3) exposure to study drug: 25.6 wk (24.7, 26.6)

Baseline Characteristics

		B/F/TAF N=24
Median age, y (range)		15 (12–17)
Median weight, kg (Q1, Q3)		48.9 (42.2, 56.4)
Female, n (%)		19 (79)
Race, n (%)	Asian	9 (39)
	Black	12 (52)
	White	1 (4)
	Other	2 (8)
Country, n (%)	South Africa	9 (38)
	Thailand	9 (38)
	USA	6 (25)
HIV-1 RNA <50 copies/mL, n (%)		24 (100)
Mean CD4 cell count, /uL (Q1, Q3)		708 (553, 893)
Median eGFR, mL/min/1.73 m^2 (Q1, Q3)		142.5 (131.5, 153.5)
Mode of transmission, n (%)	Vertical	21 (88)
	Unknown	2 (8)
	Horizontal	1 (4)

Intensive Pharmacokinetic Data

	PK Parameter*	Cohort 1 12–<18 y; ≥35 kg N=24	B/F/TAF-Treated Adults N=1193[†]	Adolescent/Adult GMR% (90% CI)
BIC	AUC_{tau}, h·ng/mL	109,668 (31)	102,001 (27)	107 (97, 118)
	C_{max}, ng/mL	8087 (30)	6146 (23)	130 (119, 143)
	C_{tau}, ng/mL	2327 (49)	2610 (35)	86 (74, 100)
FTC	AUC_{tau}, h·ng/mL	13,579 (22)	12,294 (29)	113 (102, 124)
	C_{max}, ng/mL	2689 (34)	2127 (35)	127 (111, 145)
	C_{tau}, ng/mL	64 (25)	96 (37)	69 (62, 78)
TAF	AUC_{tau}, h·ng/mL	271 (50)	229 (63)	125 (102, 153)
	C_{max}, ng/mL	262 (45)	277 (62)	101 (80, 128)

*Mean (% coefficient of variation) unless otherwise noted; †Pooled population-PK data from 4 Phase 3 studies in HIV-infected adults. AUC_{tau}, area under curve over dosing interval; CI, confidence interval; C_{max}, maximum concentration; C_{tau}, trough concentration; GMR, geometric mean ratio.

- Similar BIC exposures were observed in adolescents and adults
- Exposures of FTC and TAF were within the safe and efficacious ranges of historical data in adults and adolescents following administration of approved F/TAF-containing products[7,8]

Overall Safety

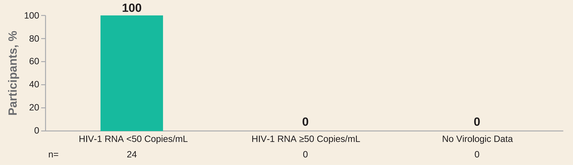
Participants, n (%)	B/F/TAF N=24
Any grade AE	15 (63)
Grade 3/4 AE	0
AE related to study drug	1 (4)
Serious AE	1 (4)
AE leading to study drug D/C	0
Death	0

- Most common AEs were upper respiratory tract infection (n=5 [21%]), and abdominal pain, body tinea, diarrhea, headache, influenza, pharyngitis, and rhinitis allergic (each n=2 [8%])
  - None of these AEs were considered related to study drug
  - No other AE occurred in >1 participant
  - All AEs were mild–moderate in severity
- 1 participant had an AE considered related to study drug: Grade 1 vomiting that began on Day 1 and resolved on the same day without dose adjustment or suspension of B/F/TAF
- 1 participant had a serious AE: Grade 2 abdominal pain that began on Day 124 and resolved on Day 132, was not related to study drug, and resolved without dose adjustment or suspension of B/F/TAF
- Most common Grade 3/4 laboratory abnormality was hematuria (n=4 [19%])
  - All 4 participants were female (aged 13–16 y) and remained on study drug: 3 were reported to have menses at the time of hematuria
  - No other Grade 3/4 laboratory abnormality was reported

Estimated Glomerular Filtration Rate (Schwartz)

- Median changes in eGFR ranged from -8.0 to -14.0 mL/min/1.73 m^2 between Weeks 2 and 24
- Changes in eGFR in female adolescents were:
  - Not considered to be clinically significant
  - Consistent with Phase 3 adult data, and the known effect of BIC on organic cation transporter 2 and multidrug and toxin extrusion protein 1, with no effect on actual GFR

Efficacy: Virologic Outcome

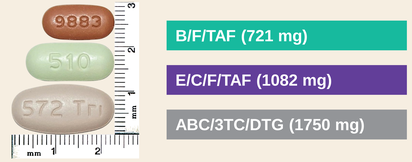


- Maintenance of virologic suppression at Week 24: HIV-1 RNA <50 copies/mL in all 24 participants (100%)
- Mean change in CD4 cell count at Week 24: +53 cells/μL (standard deviation 197.0)
- No participants met the criteria for resistance analysis

Participant-Reported Palatability and Acceptability

- All 24 participants reported B/F/TAF was palatable, and its shape and size were acceptable
- 21 participants (88%) were ≥95% adherent through Week 24

INSTI-Containing Single-Tablet Regimen Size Comparisons*



*Comparative tablet sizes of B/F/TAF and integrase inhibitor-containing single-tablet regimens approved in USA for adolescent use; *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 HIV-1–infected adolescents (aged 12–<18 y; weight ≥35 kg):
  - B/F/TAF was well tolerated
    - All AEs were mild–moderate, with only 1 AE considered related to B/F/TAF and only 1 serious AE
    - There were no deaths, pregnancies, or AEs that led to D/C
  - B/F/TAF demonstrated high rates of maintained virologic suppression
  - Exposures of BIC, FTC, and TAF were consistent with the ranges of exposures observed in adults in Phase 3 trials of B/F/TAF
  - Efficacy and safety were consistent with results from Phase 3 trials of B/F/TAF in adults, which showed high proportions with viral suppression and no resistance
- These data support further pediatric studies of B/F/TAF, which may be an important unboosted INSTI option for HIV-infected adolescents and children due to high barrier to resistance, small tablet size, low potential for drug-drug interactions, and lack of food requirement

References

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