Safety, Pharmacokinetics, and Efficacy of FTC/TAF in HIV-Infected Adolescents (12–18 years)

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Introduction

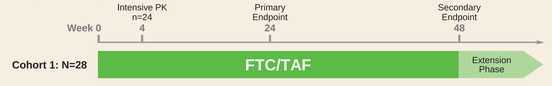
- The fixed-dose combination of emtricitabine (FTC)/tenofovir alafenamide (TAF) is approved for adolescents (USA and EU) and is a recommended 1st-line nucleoside reverse transcriptase inhibitor (NRTI) backbone for adolescents (USA)[1]
- FTC/TAF fixed-dose combination (FDC) was developed with 2 dose strengths: 200/25 and 200/10 mg[2]
  - FTC/TAF 200/10 mg coadministered with atazanavir with ritonavir (RTV [r]) or cobicistat (COBI), darunavir with RTV or COBI, or lopinavir (LPV) with RTV[3]
  - FTC/TAF 200/25 mg coadministered with dolutegravir, efavirenz (EFV), maraviroc, nevirapine, rilpivirine, or raltegravir[3]
  - FTC/TAF 200/25 mg is the only dose strength approved by the FDA[4]
- The safety and efficacy of TAF in adolescents and children have been demonstrated in studies of elvitegravir/COBI/FTC/TAF, including favorable bone and renal safety[5,6]
- The safety, pharmacokinetics (PK), and efficacy of other FTC/TAF-containing regimens in adolescents have not been reported
- This presentation reports the 1st data on the use of FTC/TAF with various 3rd agents in an HIV-1–infected, adolescent population

Objectives

- Primary:
  - To determine the plasma PK of TAF in HIV-1–infected adolescents
  - To confirm the TAF dose in HIV-1–infected adolescents virologically suppressed on a 2 NRTI-containing regimen
  - To evaluate the safety and tolerability of FTC/TAF through 24 wk
- Secondary:
  - To determine the plasma PK of FTC and the TAF metabolite tenofovir (TFV)
  - To evaluate the safety, tolerability, and efficacy of FTC/TAF through 48 wk

Methods

Study Design



- Phase 2/3, open-label, multicenter, multicohort, single-arm study (NCT02285114)
  - Cohort 1: HIV-1–infected, virologically suppressed adolescents
- Cohort 1 key inclusion criteria:
  - Aged 12–18 y; weight ≥35 kg
  - HIV-1 RNA <50 copies/mL for ≥6 mo on a stable regimen of 2 NRTIs with various 3rd antiretroviral (ARV) agents
  - CD4 count ≥200 cells/μL
  - Estimated glomerular filtration rate (eGFR; Schwartz formula) ≥90 mL/min/1.73 m^2
- FTC/TAF 200/10 mg qd with boosted or 200/25 mg qd with unboosted 3rd ARVs
- Safety assessments:
  - Adverse events (AEs) and clinical laboratory abnormalities
  - Bone mineral density (BMD) and Z-score every 24 wk
- Efficacy assessments: HIV-1 RNA and CD4 cell count
- PK assessment: steady-state plasma PK parameters calculated for TAF, FTC, and TFV

Results

Disposition

- Screened: N=37; enrolled: N=28
- No study drug discontinuations (D/C) through Week 24
- Median (quartile [Q] 1, Q3) exposure to study drug: 75.8 wk (55.9, 129.3)

Baseline Characteristics

		FTC/TAF (N=28)
Median age, y (range)		14 (12–17)
Median weight, kg (Q1, Q3)		45.3 (35.1, 62.4)
Male, n (%)		16 (57)
Race, n (%)	Asian	1 (4)
	Black	12 (43)
	White	3 (11)
	Other	12 (43)
Countries, n (%)	Panama	12 (43)
	South Africa	10 (36)
	USA	6 (21)
HIV-1 RNA <50 copies/mL, n (%)		27 (96)
Mean CD4 cell count, /μL (SD)		909 (242.7)
Mean CD4 % (SD)		36.1 (6.40)
Median eGFR, mL/min/1.73 m^2 (Q1, Q3)		156.8 (138.6, 188.8)
Mode of transmission, n (%)	Vertical	24 (86)
	Unknown	2 (7)
	Heterosexual sex	3 (11)

SD, standard deviation.

Intensive PK Data by TAF Dose, Regardless of 3rd Agent*

TAF Dose		Adolescent n	Adolescent AUC_{tau}, h·ng/mL	Adult n	Adult AUC_{tau}, h·ng/mL†	% GLSM Ratio (90% CI)
TAF	FTC/TAF 200/25 mg	9	201 (41.8)	161	167 (32.7)	117 (93.7, 147)
	FTC/TAF 200/10 mg	9	140 (80.9)	131	101 (60.2)	116 (72.2, 185)
TFV	FTC/TAF 200/25 mg	11	193 (24.2)	176	356 (37.2)	56 (49.0, 64.2)
	FTC/TAF 200/10 mg	13	416 (25.5)	152	336 (43.1)	128 (113, 145)

*Mean (% coefficient of variation [CV]) unless otherwise noted; †From population-PK data from a Phase 3 study in HIV-infected adults. AUC_{tau}, area under curve over dosing interval; CI, confidence interval; GLSM, geometric least-squares mean.

- Mean (%CV) FTC AUC_{tau} values were 14,300 (42.5) h·ng/mL in FTC/TAF 200/25-mg group and 14,800 (30.3) h·ng/mL in FTC/TAF 200/10-mg group

Intensive PK Data by 3rd Agent*

Regimen		Adolescent n	Adolescent AUC_{tau}, h·ng/mL	Adult n	Adult AUC_{tau}, h·ng/mL†	% GLSM Ratio (90% CI)
TAF	FTC/TAF 200/25 mg + EFV	9	201 (41.8)	6	142 (127)	134 (102, 175)
	FTC/TAF 200/10 mg + LPV/r	9	140 (80.9)	15	89.8 (25.0)	119 (72.2, 195)
TFV	FTC/TAF 200/25 mg + EFV	11	193 (24.2)	8	312 (92.9)	74.2 (50.4, 109)
	FTC/TAF 200/10 mg + LPV/r	13	416 (25.5)	17	418 (44.2)	103 (85.4, 125)

*Mean (% CV) unless otherwise noted; †From population-PK data from a Phase 3 study in HIV-infected adults.

- Exposures of TAF, FTC, and TFV (regardless of 3rd agent) were within the safe and efficacious ranges of historical data in adults and adolescents following administration of approved FTC/TAF-containing products[7]

Overall Safety

Participants, n (%)	FTC/TAF (N=28)
AE	24 (86)
Grade 3/4 AE*	3 (11)
AE related to study drug†	5 (18)
Serious AE	2 (7)
AE leading to study drug DC	0
Death	0

*Gastrointestinal disorders (n=2) and syncope (n=1); none were considered study drug related; †Vomiting (n=1), chills (n=1), headache (n=3), dysgeusia (n=1), and syncope (n=1).

Adverse Events

>2 Participants, n (%)	FTC/TAF (N=28)
Viral upper respiratory tract infection	9 (32)
Headache	7 (25)
Vomiting	5 (18)
Diarrhea	4 (14)
Acne	6 (21)
Rhinitis (allergic)	3 (11)
Upper respiratory tract infection	3 (11)

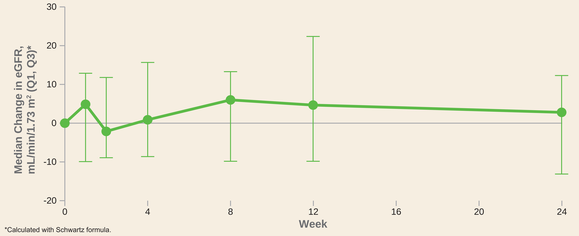
- No AE event led to study drug D/C

Grade 3/4 Laboratory Abnormalities

>1 Participant, n (%)	FTC/TAF (N=28)
Amylase*	5 (18)
Low density lipoprotein (fasting)	2 (7)
Hematuria†	2 (7)

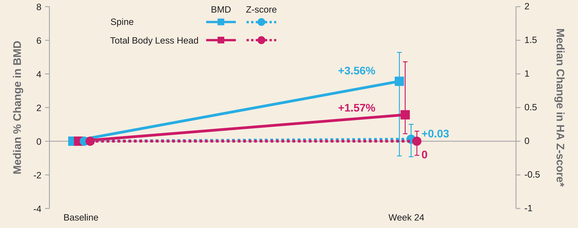
*All amylase elevations were asymptomatic and considered not clinically significant; †All participants with hematuria were female (aged 13–17 y) and were reported to have menses at time of hematuria.

Changes in Estimated Glomerular Filtration Rate



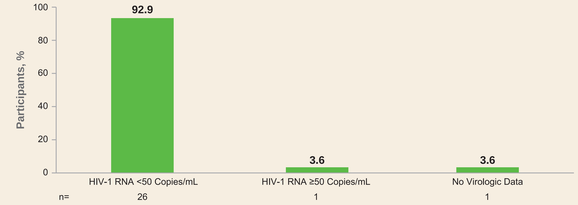
*Calculated with Schwartz formula.

Changes in Bone Mineral Density and Z-score



*For BMD Z-scores, height for age (HA) instead of chronologic age was used; HA was determined as age at which participant's height was median stature using age-growth charts.[8]

Efficacy: Virologic Outcome



- Maintenance of suppression at Week 24:
  - HIV-1 RNA <50 copies/mL: 92.9% (26/28)
- CD4 cell count at Week 24:
  - Mean (SD) change in CD4 cell count: −130 (272.6) cells/μL
    - Mean (SD) CD4 count at baseline was 909 (242.7) cells/μL and at Week 24 was 779 (255.1) cells/μL
  - Mean (SD) change in CD4 %: −0.2% (3.84%)
- No participant met the criteria for resistance analysis

Adherence and Palatability: Week 24

- Mean 93% (SD 10%) adherence
- 71% (20/28) of participants were ≥95% adherent
- All 28 participants reported that study drug was palatable

Conclusions

- In HIV-1–infected adolescents (aged 12–<18 y; weight ≥35 kg):
  - FTC/TAF in combination with various 3rd ARV agents maintained high rates of virologic suppression
  - FTC/TAF was well tolerated
    - There were no deaths, pregnancies, or AEs that led to DC, and no study drug-related serious AEs
    - At Week 24, there was little change in CD4 %, consistent with the high degree of virologic suppression
  - FTC/TAF resulted in increased BMD over 24 wk and minimal changes in spine or total body less head Z-scores
  - Exposures of TAF, FTC, and TFV were consistent with those in adults
- These results support the use of FTC/TAF as a safe and effective NRTI backbone in combination with various 3rd agents for the treatment of HIV-1 infection in adolescents

References

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