Pharmacokinetics, Safety, and Efficacy of E/C/F/TAF in HIV-1-Infected Children (6 to <12 years)

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Introduction

- For HIV-infected children (aged <12 y), antiretroviral therapy treatment options are limited[1]
  - No once-daily single-tablet regimen is available
- Tenofovir disoproxil fumarate (TDF) is associated with bone and renal toxicities
  - Plasma exposure has been linked to the toxicity
  - Not considered as 1st-line nucleos(t)ide reverse transcriptase inhibitor in children
- Tenofovir alafenamide (TAF) results in 91% lower plasma tenofovir (TFV) exposures than TDF[2]
- In adults and adolescents, TAF has a better renal and bone safety profile than TDF[2,3]
- Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/TAF (E/C/F/TAF; available formulation: 150/150/200/10 mg):
  - Once-daily, integrase strand transfer inhibitor (INSTI)-containing single-tablet regimen
  - Recommended as initial regimen in adults and adolescents[4]
- E/C/F/TAF may have potential benefits for HIV-1-infected children

Objectives

- In HIV-1-infected children:
  - Primary objectives
    - To determine plasma pharmacokinetics (PK) of EVG and TAF
    - To evaluate safety and tolerability of E/C/F/TAF through 24 wk of treatment
  - Secondary objectives
    - To evaluate safety and efficacy of E/C/F/TAF through 48 wk
    - To determine plasma PK of COBI, FTC, and TFV

Methods

Study Design

- Phase 2/3, single-arm, open-label, switch study (NCT01854775)
- HIV-1-infected, virologically suppressed children on stable antiretroviral therapy
- Key inclusion criteria:
  - Aged 6 to <12 y
  - Weight ≥25 kg
  - HIV-1 RNA <50 copies/mL for ≥6 mo
  - CD4 count >100 cells/μL
  - Estimated glomerular filtration rate (eGFR; Schwartz formula) ≥90 mL/min/1.73m^2
  - Able to swallow tablets
- PK assessments
  - EVG, COBI, FTC, TAF, and TFV PK determined at steady state
  - Exposures in children compared with historical data in adults
- Safety assessments:
  - Adverse events (AEs) and clinical laboratory abnormalities
  - Bone mineral density (BMD) and Z-score every 24 wk
- Efficacy assessment
  - HIV-1 RNA
  - CD4 cell count

Results

Study Disposition

- Screened: N=26; enrolled: N=23
- No study drug discontinuations through Week 24

Baseline Characteristics*

		E/C/F/TAF N=23
Age, y		10 (8–11)
Female		14 (61)
Country of origin	Uganda	14 (61)
	US	6 (26)
	Thailand	3 (13)
Race	Black	18 (78)
	White	2 (9)
	Asian	3 (13)
Height, cm		136 (120–150)
Height Z-score		−0.43
Weight, kg		31 (26–58)
Weight Z-score		−0.25
eGFR (Schwartz), mL/min/1.73m^2		150 (99–182)
HIV-1 RNA <50 copies/mL		23 (100)
CD4 count, cells/μL		969 (603–1421)
Time since diagnosis, y		8 (6–11)
Mode of infection: vertical transmission		23 (100)

*Data are median (range) or n (%), unless stated otherwise.

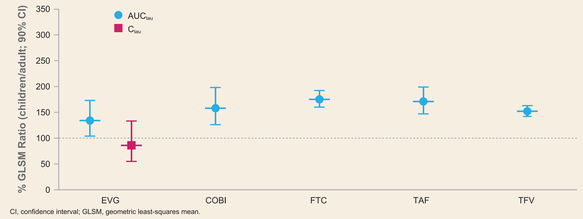
Intensive Pharmacokinetic Data

	Parameter*	Children†	Adults‡
EVG	AUC_{tau}, h·ng/mL	33,800 (58)	22,800 (34)
	C_{tau}, ng/mL	370 (119)	290 (62)
COBI	AUC_{tau}, h·ng/mL	15,900 (52)	9500 (34)
FTC	AUC_{tau}, h·ng/mL	20,600 (19)	11,700 (17)
TAF	AUC_{tau}, h·ng/mL	333 (45)	210 (79)
TFV	AUC_{tau}, h·ng/mL	440 (21)	290 (27)

*All data are mean (% coefficient of variation); †n=22 for EVG and FTC AUC_{tau}, n=20 for COBI AUC_{tau}, and n=23 for other PK parameters; ‡From Genvoya package insert[5]; n=19 for EVG, FTC, and COBI, n=539 for TAF, and n=841 for TFV.

- Mean EVG C_{tau} was ~8x above the protein binding adjusted IC_{95}

Intensive Pharmacokinetic Data: Children vs Adults



CI, confidence interval; GLSM, geometric least-squares mean.

- Exposures of EVG, COBI, FTC, TAF, and TFV were generally higher than those of adults but within the safe and efficacious range of exposures established in E/C/F/TAF and/or E/C/F/TDF clinical development programs

Summary of Adverse Events

n (%)	E/C/F/TAF N=23
Any AE	17 (74)
Study drug related	9 (39)
Grade 3 or 4	0
Serious AE or death	0
Study drug discontinuation due to AE	0

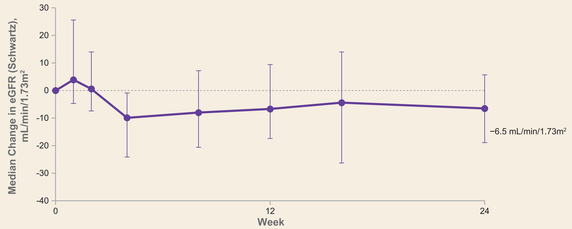
Study Drug-Related Adverse Events

n (%)	E/C/F/TAF N=23
Study drug-related AE*	9 (39)
Abdominal pain	4 (17)
Vomiting	4 (17)
Constipation	1 (4)
Vitamin D deficiency	1 (4)
Dizziness	1 (4)
Headache	1 (4)
Product shape issue	1 (4)
Product size issue	1 (4)

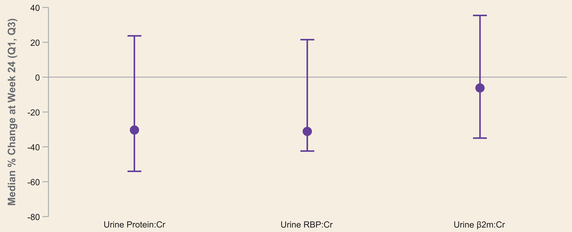
*Participants may have had >1 study drug-related AE.

- No cases of proximal renal tubulopathy

Changes in eGFR

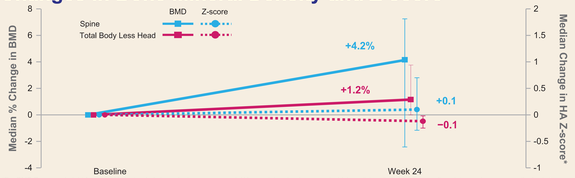


Changes in Renal Biomarkers



Cr, creatinine; RBP, retinol binding protein; β2m, β2-microglobulin; Q, quartile.

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.[6]

Efficacy

- Virologic outcome
  - At Week 24, HIV-1 RNA was <50 copies/mL in 100% of participants
- CD4 cell count
  - Median change in CD4 cell count at Week 24: −130 cells/μL
  - Median change in CD4% at Week 24: −2.1%
  - Median CD4 cell count at Week 32: 849 cells/μL

Participant-Reported Palatability and Acceptability

- Almost all participants (n=21) reported that study drug was palatable, and its shape and size (19 mm x 8.5 mm) were acceptable
  - 1 participant reported study drug to be unpalatable
  - Another participant reported size to be unacceptable
  - Both participants continued to take the tablet

Conclusions

- In children (aged 6 to <12 y; weight ≥25 kg):
  - E/C/F/TAF maintained high rates of virologic suppression
  - E/C/F/TAF was well tolerated, with no discontinuations due to AEs
  - E/C/F/TAF had minimal impact on BMD
  - Renal safety profile of E/C/F/TAF was consistent with adults
    - Improvement in markers of proteinuria
    - No cases of proximal renal tubulopathy
  - Exposures of E/C/F/TAF and TFV were modestly higher than in adults
- These results support E/C/F/TAF as the 1st once-daily INSTI-based single-tablet regimen in children

References

1. http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118951.htm; **2.** Sax PE, et al, Lancet 2015;385:2606-15; **3.** Gaur AH, et al, Lancet HIV 2016;3:e561-8; **4.** http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf; **5.** Genvoya [package insert]. **6.** http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/index.htm.

Acknowledgments

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