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Disclosures

- **Dr. Natukunda reports no conflicts**

Introduction

- Children weighing <25 kg with HIV have few ARV options; no STR is used or approved for this population in the US or EU
- TAF has 91% lower plasma TFV exposures than TDF[1]
  - Lower TFV exposure with TAF is associated with improved renal and bone safety in adults, adolescents and children[1,2]
  - TDF is not a recommended first-line NRTI for children
- E/C/F/TAF (available formulation: 150/150/200/10 mg):
  - Once-daily, INSTI-containing STR
  - Recommended as initial regimen in the US in adults, adolescents, and children aged ≥6 y and weighing ≥25 kg[3]
- E/C/F/TAF has been formulated as a low-dose STR for children aged ≥2 y and weighing 14–<25 kg
  - Low-dose STR strength is E/C/F/TAF 90/90/120/6 mg (60% of full-strength STR)
- This is the first study to report the PK, safety, and efficacy of E/C/F/TAF in young children aged ≥2 y living with HIV

ARV, antiretroviral; E/C/F/TAF, elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PK, pharmacokinetics; STR, single tablet regimen; TFV, tenofovir; TDF, tenofovir disoproxil fumarate.

1. Sax PE, et al. Lancet 2015;385:2606-15; 2. Gaur AH, et al. Lancet HIV 2016;3:e561-8; 3. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. 4. Natukunda E, et al. Lancet Child Adolesc Health. 2017 ;1:27-34.

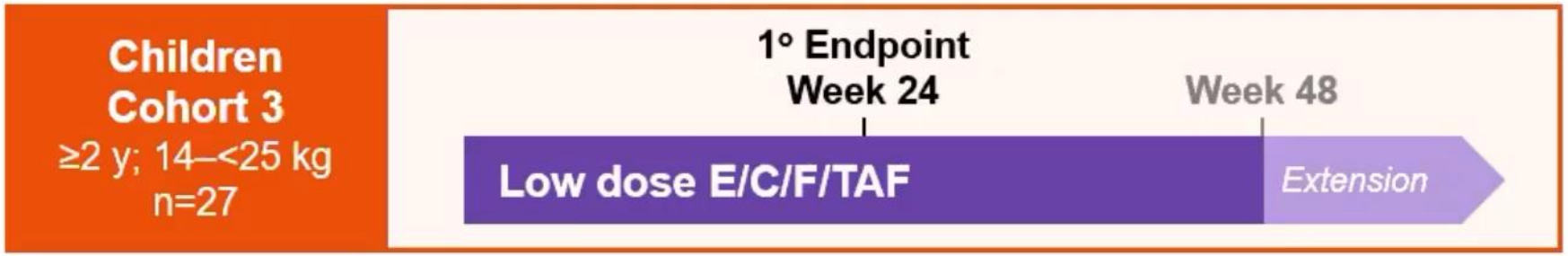
Important Note

- **Due to COVID-19, some data were not available for this presentation**

Phase 2/3, Open-label, Multicenter, Multi-cohort, Single-arm Study (NCT01854775)

Eligibility Criteria

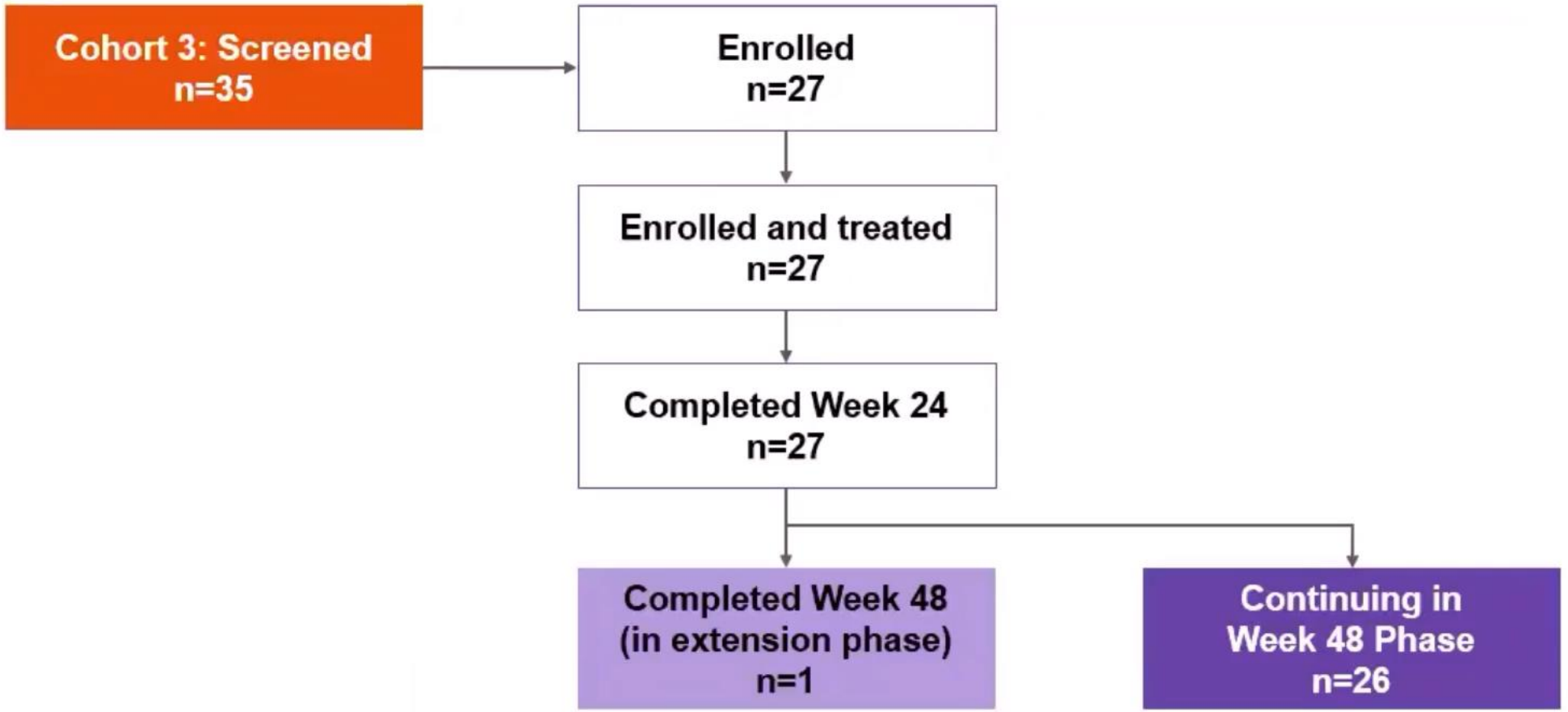
- HIV-1 RNA <50 copies/mL for ≥6 mo
- CD4 count ≥400 cells/μL
- eGFR ≥90 mL/min/1.73 m^2 (Schwartz)



- Cohort 1 (n=50): adolescent, 12–<18 y, ≥35 kg; received full strength E/C/F/TAF
  - Part A: intensive PK assessed to confirm E/C/F/TAF dose
  - Part B: after dose confirmation/IDMC review of short-term safety (Part A), more participants were enrolled to complete cohort, initiate enrollment into next-younger cohort
- Cohort 2 (n=50): children, 6–<12 y, ≥25 kg; received full strength E/C/F/TAF
  - Part A: intensive PK assessed to confirm E/C/F/TAF dose
  - Part B: after dose confirmation/IDMC review of short-term safety (Part A), more participants were enrolled to complete cohort, initiate enrollment into next-younger cohort

IDMC, independent data monitoring committee; eGFR, estimated glomerular filtration rate.

Part A Disposition: PK Substudy

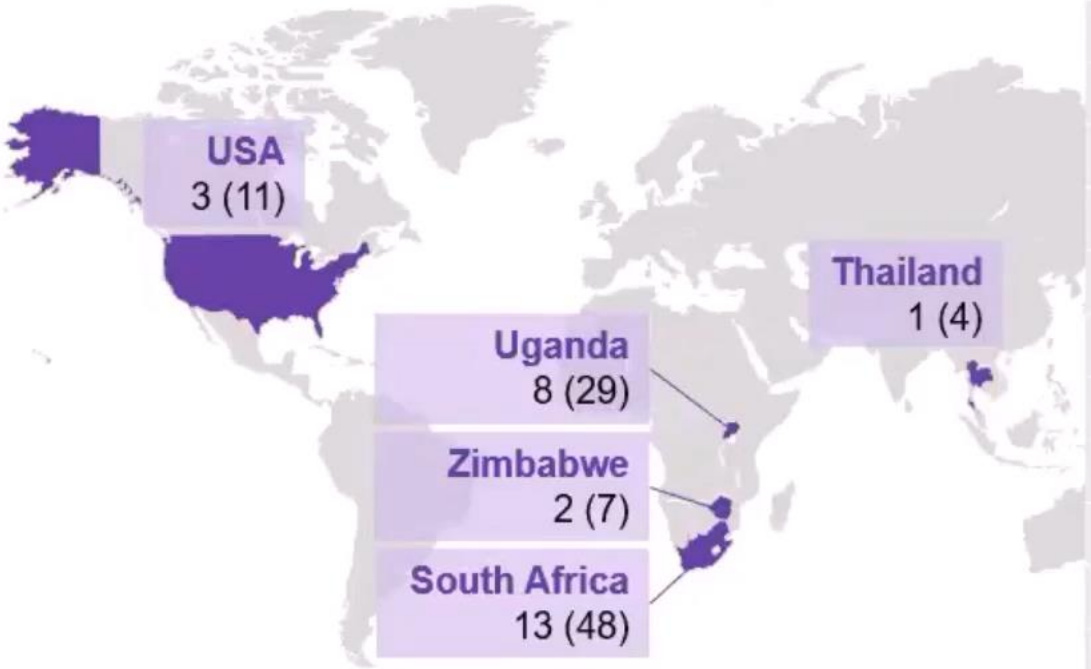


- Median (Q1, Q3) duration of exposure: 24.1 wk (24.1, 32.1)

Q, quartile.

Baseline Characteristics

Enrollment by Country, n (%)



	Children ≥2 y, 14–<25 kg n=27
Median age, y (range)	6 (3–9)
Median weight, kg (range)	19.3 (14.6–23.5)
Female, n (%)	17 (63)
Race, n (%)	
Asian	2 (7)
Black	24 (89)
HIV-1 RNA <50 copies/mL, n (%)	27 (100)
Median CD4 cell count/μL (Q1, Q3)	1061 (895, 1315)
Median CD4% (Q1, Q3)	37.4 (30.6, 40.3)
Median eGFR, mL/min/1.73 m^2 (Q1, Q3)	147.0 (139.1, 159.1)
Vertical transmission, n (%)	25 (93)
Previous ARVs, n (%)	
NRTIs (ABC, AZT, 3TC, FTC, TDF)	20 (74)
INSTI (RAL)	1 (4)
NNRTI (NVP or EFV)	4 (15)
PI (LPV/r, DRV/r)	15 (56)

3TC, lamivudine; ABC, abacavir; AZT, zidovudine; EFV, efavirenz; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir.

Intensive PK Data: E/C/F/TAF Low-Dose Tablet

	PK Parameter*	Cohort 3 ≥2 y; ≥14 kg N=27	E/C/F/TAF-Treated Adults N=1193†	Children/Adults %GLSM Ratio (90% CI)
EVG	AUC_{tau}, h·ng/mL	29900	21600	**139 (112, 172)**
	C_{max}, ng/mL	2850	2000	143 (113, 180)
	C_{tau}, ng/mL	195	248	78.9 (53.1, 117)
TAF	AUC_{tau}, h·ng/mL	344	178	**193 (166, 224)**
	C_{max}, ng/mL	218	145	150 (116, 195)

*Geometric least squares mean (GLSM); †EVG: n=19 from intensive PK data (1 Phase 2 study in adults with HIV; TAF: n=539 from population PK data (2 Phase 3 studies in adults with HIV).

- EVG and TAF geometric mean AUC_{tau} estimates were modestly (<2-fold) higher in children vs adults
- EVG C_{tau} slightly lower in children than adults, but still 9-fold above IC_{50} for wild-type virus
- Exposures of EVG and TAF were within safe and efficacious ranges of historical data in adults, adolescents, and children following administration of E/C/F/TAF at the available strength
- Exposures of COBI, FTC and TFV also remained within range of historical data

IC_{50}, half-maximal inhibitory concentration.

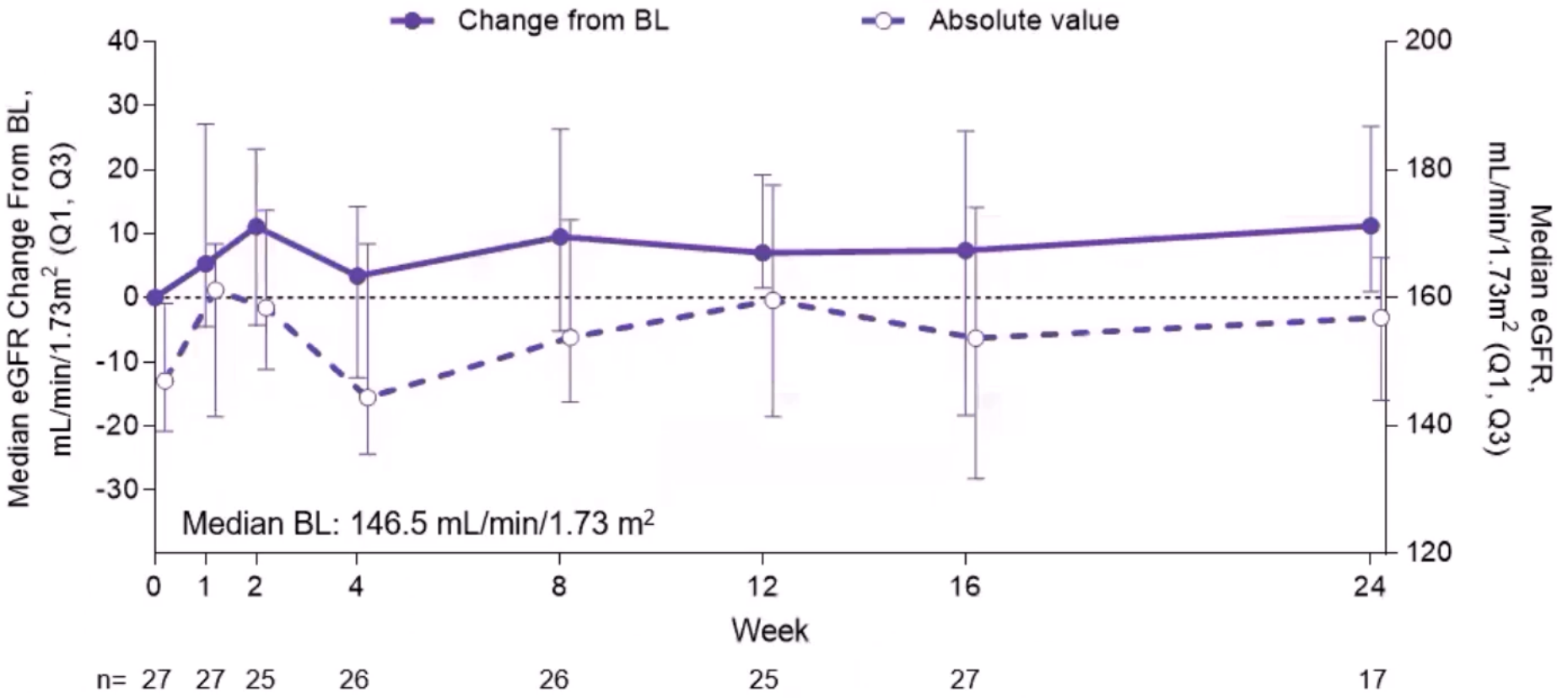
Overall Safety

Participants, n (%)	Children ≥2 y, 14–<25 kg n=27
Any grade AE	19 (70)
Grade 3 or 4 AE	0
AE related to study drug	4 (15)*
Serious AE	1 (4)
AE leading to study drug discontinuation	0
Death	0

- Most common AEs were upper respiratory tract infection (n=6 [22%]), cough (n=5 [19%]), decreased appetite (n=4 [15%]), vomiting (n=4 [15%])
  - No other AE occurred in >3 participants and all AEs were mild–moderate in severity
- 4 participants had AEs considered related to study drug: diarrhea (n=2), vomiting (n=2), asthenia (n=1), decreased appetite (n=1)
- 1 participant had a serious AE (pneumonia), not considered related to study drug
- Grade 3 or 4 laboratory abnormalities: Grade 3 decreased platelets (n=1 [4%])

*1 participant may have had >1 AE.

Estimated Glomerular Filtration Rate (Schwartz)



- eGFR remained stable through Week 24

BL, baseline.

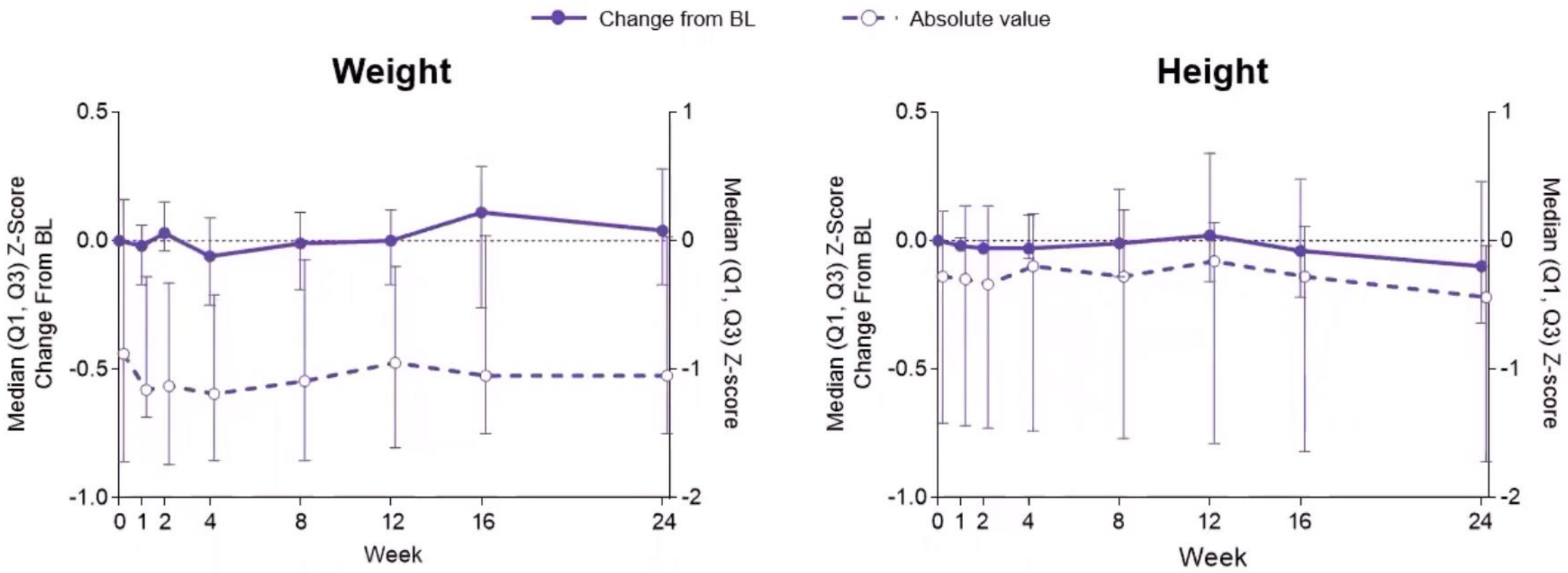
Changes in Spine and TBLH BMD

	BMD	
Median (Q1, Q3)	**Spine**	**TBLH**
Baseline	0.436 g/cm^2 (0.391, 0.468)	0.478 g/cm^2 (0.442, 0.513)
% Change at Week 24 (n=12)	+4.243 (0.701, 6.852)	+4.224 (2.120, 5.379)

BMD, bone mineral density; TBLH, total body less head.

- No participants had ≥4% decline in spine or TBLH BMD

Changes in Body Weight and Height Z-Scores



Through Week 24:

- Body weight was consistently below the reference population
- Height remained similar to reference population

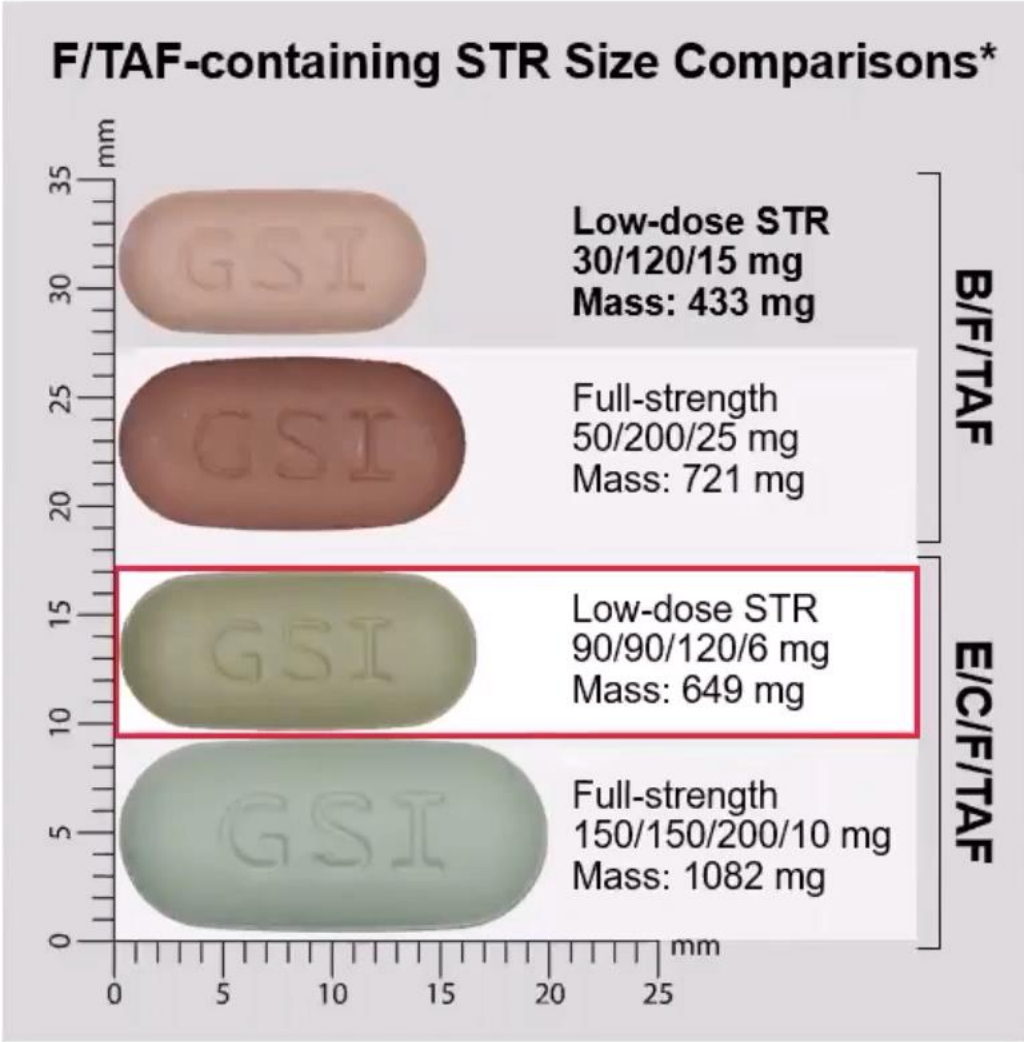
Efficacy: Virologic Outcome

- Using a missing = excluded analysis, virologic suppression (HIV-1 RNA <50 copies/mL) was maintained in all 27 participants (100%) at Week 16
  - 16 of 17 participants (94%) at Week 24
- Mean (SD) CD4 cell count:
  - Baseline: 1153 (460) cells/μL
  - Change from baseline at Week 24: -137 cells/μL (278)
- Mean (SD) CD4% mean change:
  - Baseline: 35.9 (6.73)
  - Change from baseline at Week 24: 0.0 (4.40)
- No participants met the criteria for resistance analysis

SD, standard deviation.

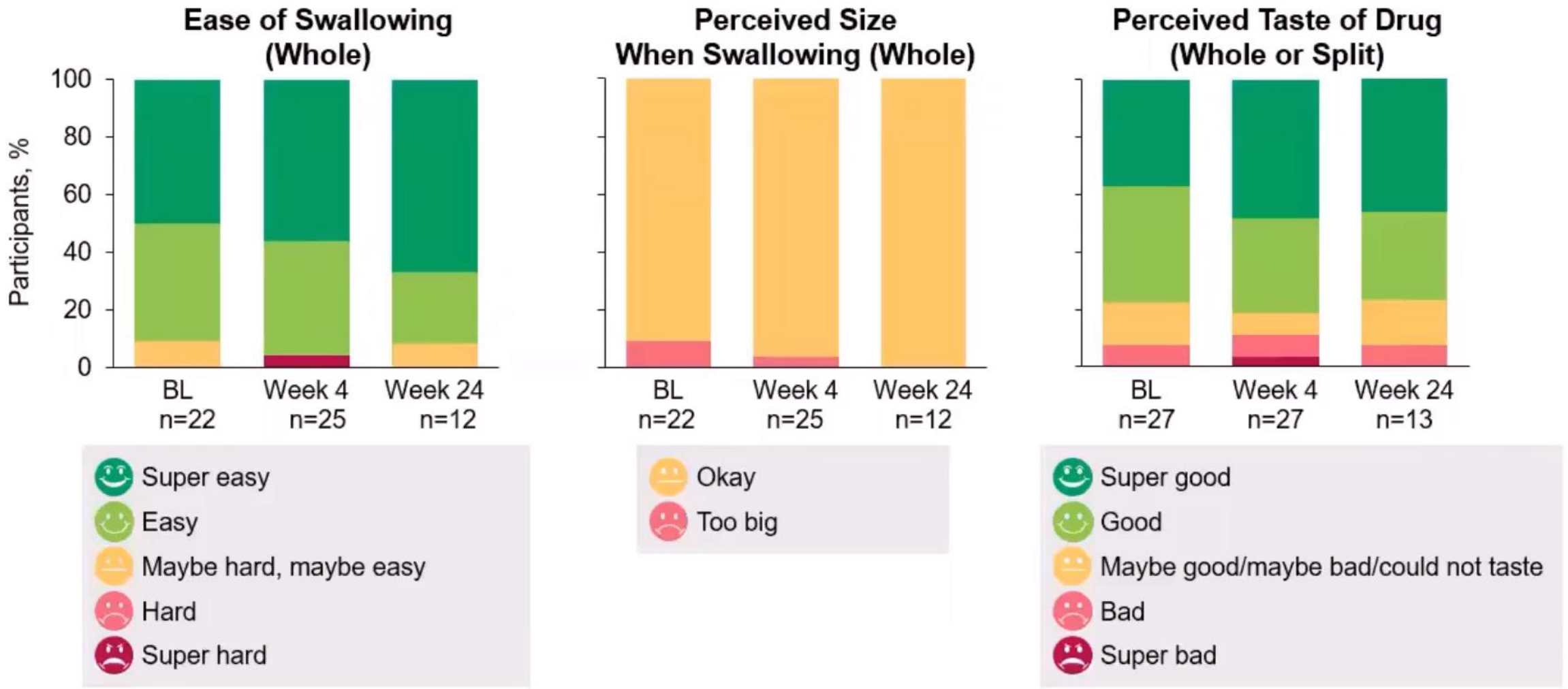
Tablet Size and Adherence

- Palatability and acceptability assessments:
  - Questionnaire to ask the participant/parent:
    - Whether tablet was broken in half to allow it to be swallowed
    - If broken in half, whether both halves were taken within 10 min
  - Facial scale and age-appropriate labels to rate:
    - Ease or difficulty in swallowing tablet (if tablet was taken whole only)
    - Acceptability of tablet shape
    - Acceptability of tablet size
    - Assessment of tablet taste
- Mean (SD) adherence to E/C/F/TAF was 97% (3%)



*Approved in USA for use in adults, adolescents, and children weighing ≥25 kg; final commercial trade dress may change (note: tablet size is not intended to compare clinical efficacy and safety, indications, dosing regimens, or treatment adherence).

Acceptability and Palatability



- Numbers of children who split tablet: n=4 (BL), n=2 (Week 4), and n=1 (Week 24)
- For children who had tablet split, all were able to take both halves one right after the other (within 10 min)

Conclusions

- In virologically suppressed children (aged ≥2 y; weight ≥14–<25 kg):
  - The E/C/F/TAF low-dose STR was well tolerated
    - All AEs were mild–moderate, and there were no AEs that led to discontinuation
  - E/C/F/TAF demonstrated excellent adherence and maintained virologic suppression
  - The low dose tablet had a high level of acceptability (taste and swallowability)
  - Exposures of EVG and TAF were consistent with the ranges of exposures observed in adults in Phase 3 trials of E/C/F/TAF
- Efficacy and safety were consistent with results from Phase 3 trials of E/C/F/TAF in adults, which showed high proportions with viral suppression, no resistance, and good tolerability
- These data support further pediatric studies of E/C/F/TAF, which may be an important INSTI option for HIV-infected young children aged ≥2 y and able to swallow a tablet

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