Poster Number

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Safety, Efficacy and Pharmacokinetics of the Integrase Inhibitor-Based E/C/F/TAF Single-Tablet Regimen in Treatment-Naïve HIV-Infected Adolescents Through 24 Weeks of Treatment

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Background

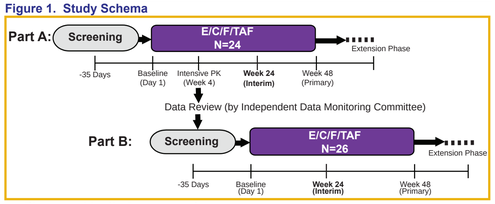
- E/C/F/TAF is a novel integrase inhibitor-based single-tablet regimen (STR) containing the novel tenofovir prodrug tenofovir alafenamide (TAF)
- The adult and adolescent formulation of E/C/F/TAF contains elvitegravir (EVG) 150 mg, cobicistat (COBI) 150 mg, emtricitabine (FTC) 200 mg, and TAF 10 mg
- TAF generates ~90% lower plasma TFV concentrations than TDF
- In two phase 3 adult studies analyzed through 48 weeks, E/C/F/TAF demonstrated improvements in renal and bone safety (Sax CROI 2015, #143LB)[1] and noninferior efficacy to Stribild (Wohl CROI 2015, #113LB)[2]
- The EVG dose of 150 mg was previously confirmed in adolescents (Gaur 2010)[3]
- E/C/F/TAF may have potential benefits for HIV-infected adolescents[4]:
  - Improved renal safety profile
  - Improved bone safety during development of peak bone mass and subsequent lifelong ART
  - Potential for improved adherence from once-daily STR dosing
  - Activity against HIV with NNRTI or PI resistance mutations
  - Improved safety during pregnancy

Design and Objectives

- Phase 2/3, single-arm, open-label, two-part study
- HIV-infected treatment-naïve adolescents (12-18 years), n = 50
- Key Enrollment Criteria:
  - HIV-1 RNA ≥ 1000 copies/mL
  - Genotypic sensitivity to EVG, FTC and TFV
  - CD4 count >100 cells/uL
  - HBV and HCV negative
  - eGFR (Schwartz formula) ≥ 90 mL/min/1.73m^2
  - Weight ≥ 35 kg
- Co-Primary Objectives:
  - Determine steady-state pharmacokinetics (PK) of EVG, TAF components of E/C/F/TAF
  - Confirm dose of E/C/F/TAF FDC
  - Evaluate safety and tolerability through 24 weeks of treatment
- Secondary Objective: evaluate efficacy (antiviral activity) of E/C/F/TAF

Methods

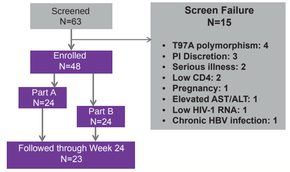
Figure 1. Study Schema



- **Pharmacokinetic Assessments:**
  - EVG, COBI, FTC, TAF and TFV PK determined at steady state by validated LC/MS/MS assays
  - TAF and TFV compared to adult exposures using population PK modeling
  - EVG, COBI, FTC, TAF and TFV compared by geometric mean ratio (GMR) with equivalence boundary of 70% to 143% for the 90% confidence interval (CI)
- **Safety Assessments:**
  - Adverse events (AE) and clinical laboratories (CBC, chemistries, urinalysis)
  - Dual-energy X-ray absorptiometry (DXA) of spine and total body every 24 weeks, with height-adjusted Z-scores
- **Efficacy Assessments:**
  - HIV-1 RNA (Roche TaqMan 2.0) with endpoints of <50, and <400 copies/mL
  - Suboptimal Virologic Response (SVR) = <1 log decrease in HIV-1 RNA AND HIV-1 RNA ≥400 copies/mL at Week 8, confirmed at Week 12
  - Virologic Rebound (VR): Rebound from <50 to ≥400 copies/mL OR >1 log increase from nadir, confirmed at subsequent visit
  - Upon confirmed SVR or VR, genotyping and phenotyping for emergent resistance to PR, RT, IN

Methods (cont'd)

Figure 2. Disposition of Subjects



Results

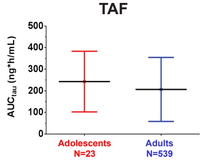
Table 1. Demographics and Baseline Characteristics

Number of subjects	N	48
Age	Years, median (range)	15 (12-17)
Sex	Male, n (%)	20 (42)
Country of Origin	Uganda, n (%)	30 (63)
	United States	9 (19)
	Thailand	6 (13)
	South Africa	3 (6)
Race	Black	42 (88)
	Asian	6 (12)
Height	cm, median (range)	157 (123-182)
	Z-score, median (Q1, Q3)	-0.62 (-1.81, 0.05)
Weight	kg, median (range)	52 (35-89)
	Z-score, median (Q1, Q3)	-0.54 (-1.21, 0.47)
eGFR (Schwartz)	mL/min/1.73m^2, median (range)	158 (101-284)

Table 2. HIV Disease Characteristics

Baseline HIV-1 RNA	$\log_{10}$ copies/mL, mean (SD)	4.62 (0.59)
	≤ 100,000 copies/mL, n (%)	38 (79)
	> 100,000 copies/mL	10 (21)
Baseline CD4 Count	cells/μL, median (range)	452 (95-1110)
	≥ 500 cells/μL, n (%)	17 (35)
	350-499	18 (38)
	200-349	9 (19)
	<200	4 (8)
Time Since Diagnosis	Years, median (range)	1 (0-14)
Mode Of Infection	Vertical transmission, n (%)	32 (67)
	Heterosexual sex	10 (21)
	Homosexual sex	6 (13)

Figure 3. TAF Pharmacokinetics: Adolescent and Adult

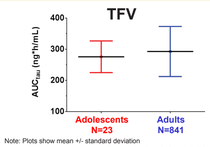


Parameter	E/C/F/TAF: Adolescents[a] Mean (%CV)	E/C/F/TAF: Adults[b] Mean (%CV)
AUCtau, ng*h/ml	242.8 (57.8)	206.4 (71.8)
Cmax, ng/ml	121.7 (46.2)	162.2 (51.1)

[a] Adolescent subjects from Study GS-US-292-0106
[b] Adult subjects from Studies GS-US-292-0104 and GS-US-292-0111
Note: Plots show mean +/- standard deviation

Results (cont'd)

Figure 4. TFV Pharmacokinetics: Adolescent and Adult



	E/C/F/TAF: Adolescents[a] Mean (%CV)	E/C/F/TAF: Adults[b] Mean (%CV)	E/C/F/TDF: Adults[c] GLSM
AUCtau, ng*h/ml	275.8 (18.4)	292.6 (27.4)	3308.0
Cmax, ng/ml	14.6 (20.0)	15.2 (26.1)	399.1
Cmin, ng/ml	10.0 (19.6)	10.6 (28.5)	65.6

[a] Adolescent subjects from Study GS-US-292-0106
[b] Adult subjects from **E/C/F/TAF** treatment arms of Studies GS-US-292-0104 and GS-US-292-0111
[c] Adult subjects from **E/C/F/TDF** PK substudy of GS-US-292-0104 and GS-US-292-0111 (N=30)
GLSM = geometric least squares mean

Note: Plots show mean +/- standard deviation

- TFV exposure (by AUC_{tau}) is >90% lower from E/C/F/TAF than E/C/F/TDF

Table 3. EVG, COBI, and FTC Pharmacokinetics

Analyte	Parameter	N	E/C/F/TAF: Adolescents Mean	E/C/F/TAF: Adolescents % CV
EVG	AUC_{tau}, ng*h/mL	24	23840	25.5
	C_{max}, ng/mL	24	2230	19.2
	C_{tau}, ng/mL	24	301	81.0*
COBI	AUC_{tau} ng*h/mL	23	8241	36.1
	C_{max}, ng/mL	24	1202	35.0
	C_{tau}, ng/mL	15	25	180.0
FTC	AUC_{tau}, ng*h/mL	24	14424	23.9
	C_{max}, ng/mL	24	2265	22.5
	C_{tau}, ng/mL	23	102	38.9

- All parameters are within the range associated with safety and efficacy in adults
- All subjects had an EVG C_{tau} above the protein-binding adjusted IC_{95} of 44.5 ng/mL

Table 4. Summary of Adverse Events

Subjects Experiencing Any:	E/C/F/TAF: Adolescents N=48, % (n)	E/C/F/TAF: Adults* N=866, % (n)
Adverse Event (AE)	81.3 (39)	89.8 (778)
Grade 3 (Severe) or higher AE	8.3 (4)	8.2 (71)
ECFTAF-Related AE	37.5 (18)	39.5 (342)
Grade 3 or higher Related AE	2.1 (1)	1.4 (12)
Serious Adverse Event (SAE)	8.3 (4)	8.1 (70)
ECFTAF-Related SAE	2.1 (1)	0.3 (3)
AE leading to E/C/F/TAF discontinuation	0	0.9 (8)
Death	0	0.2 (2)

* Adult reference population is the pooled safety population from the adult phase 3 trials 292-0104 and 292-0111;
Duration of exposure in these trials was 48 weeks; no correction for the differential exposure has been made.

Table 5. Most Frequent Adverse Events

Event	E/C/F/TAF: Adolescents N=48, % (n)
Nausea	11 (22.9)
Upper respiratory tract infection	10 (20.8)
Diarrhoea	8 (16.7)
Respiratory tract infection (NOS)	7 (14.6)
Abdominal pain	7 (14.6)
Headache	7 (14.6)
Vomiting	7 (14.6)
Abdominal pain upper	6 (12.5)
Dizziness	5 (10.4)
Vitamin D Deficiency	5 (10.4)

Events occurring in >10% of subjects are listed

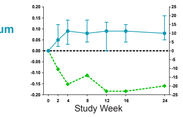
Table 6. Serum Creatinine and eGFR by Study Week

Study Week	N	Serum Creatinine, mg/dL Median	Serum Creatinine, mg/dL Median Δ from Baseline	eGFR (Schwartz), ml/min/1.73m^2 Median	eGFR (Schwartz), ml/min/1.73m^2 Median Δ from Baseline
Baseline	48*	0.57	--	157.5	--
Week 2	44	0.60	+0.05	150.5	-10.5
Week 4	43*	0.64	+0.09	140.0	-19.0
Week 8	32	0.67	+0.08	142.0	-14.0
Week 12	28	0.64	+0.09	142.0	-23.0
Week 16	23	0.63	+0.09	153.0	-23.0
Week 24	23	0.63	+0.08	148.0	-20.0

N for Cystatin C = 47 at Baseline and 42 at Week 4

Figure 5. Serum Creatinine and eGFR by Study Week

Median change in serum creatinine, mg/dL



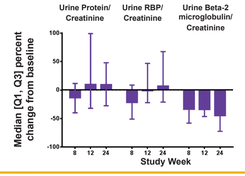
Median change in eGFR, mL/min/1.73m^2

Table 7. Renal Laboratory Assessements by Study Week

Study Week	Urine protein/creatinine, mg/g Median	Urine protein/creatinine, mg/g Median Δ from Baseline	Urine RBP/creatinine, μg/g Median	Urine RBP/creatinine, μg/g Median Δ from Baseline	Urine Beta-2 microglobulin/creatinine, μg/g Median	Urine Beta-2 microglobulin/creatinine, μg/g Median Δ from Baseline
Baseline	86.14	--	66.06	--	179.16	--
Week 2	77.84	-9.02	*Not done*		*Not done*	
Week 4	75.14	-5.75	*Not done*		*Not done*	
Week 8	54.02	-3.73	44.29	-11.22	107.02	-59.45
Week 12	81.25	8.39	52.50	-0.92	125.19	-28.33
Week 16	84.78	5.53	*Not done*		*Not done*	
Week 24	57.75	3.89	49.58	5.52	100.00	-66.17

Note: N varies by assay and timepoint but is 23 or greater for all values

Figure 6. Renal laboratory Assessements by Study Week



Serious Adverse Events

- One SAE assessed as related:
  - 13yo perinatally infected Ugandan female with moderate intermediate uveitis
  - associated allergic conjunctivitis and vision disorder
  - resolved completely with ophthalmic steroids
  - subject currently remains on E/C/F/TAF with normal funduscopic exam

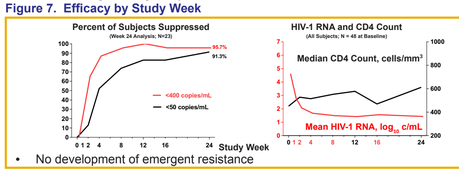
Table 8. Bone Mineral Density

Parameter:	E/C/F/TAF: Adolescents Baseline N=23	E/C/F/TAF: Adolescents Median Δ at Week 24 N=23
Spine		
Areal BMD (g/cm^2)	0.778	**+2.773%**
Z-score (unadjusted)	-1.36	-0.10
Z-score (HA)	-0.75	-0.02
≥4% decrease at Week 24, n/N	n/a	2/23
Total Body Less Head		
Areal BMD (g/cm^2)	0.856	**+0.340%**
Z-score (unadjusted)	-1.15	-0.16
Z-score (HA)	-0.66	-0.09
≥4% decrease at Week 24, n/N	n/a	0/23

Note: HA = Height-Adjusted BMD and Z-score values are medians.

- Positive median change in BMD through Week 24
- Minimal change in height-adjusted Z-scores

Figure 7. Efficacy by Study Week



- No development of emergent resistance

Table 9. Efficacy at Week 24 (Snapshot Algorithm)

Category	Adolescents (W24) N=23 % (n)	Adults (W48) N=866 %
Virologic Success at Week 24	**91.3 (21)**	**92.4**
HIV-1 RNA <50 copies/mL	91.3 (21)	92.4
Virologic Failure at Week 24	**8.7 (2)**	**3.6**
HIV-1 RNA ≥ 50 copies/mL	8.7 (2)ǂ	2.3
Discontinued due to lack of efficacy	0	0.2
Discontinued due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	0	0.9
Added new ARV	0	0.1
No Virologic Data in Week 24 Window	**0 (0)**	**4.0**
Discontinued due to AE/death	0	0.9
Discontinued due to other reasons and last available HIV-1 RNA <50 copies/mL	0	2.4
Missing data during window but on ECFTAF	0 (0)	0.7

ǂ Two subjects with HIV-1 RNA of **56** and **1010** copies/mL at W24, both **<20** copies/mL on re-test

Conclusions

- **TAF and TFV exposures in adolescents are consistent with exposures in adults.**
- **TFV exposures are ~90% lower than TFV exposures from TDF 300 mg**
- **EVG, COBI and FTC PK parameters are consistent with historical data for these agents**
- **E/C/F/TAF is well-tolerated through Week 24:**
  - **Mild drug-related GI and CNS AEs, with no discontinuations due to AEs**
  - **Slight increase in Cr consistent with COBI inhibition of tubular secretion of creatinine**
  - **Decreases in renal inflammation as measured by urine Beta-2 microglobulin**
  - **Average increase in BMD with minimal change in height-adjusted Z-scores**
- **E/C/F/TAF exhibits high antiviral activity:**
  - **All subjects achieved suppression to <50 copies/mL at Week 24 or on re-test**
  - **No emergent resistance**
- **The available data support the continued study of E/C/F/TAF in pediatric populations**

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  W Luesomboon

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