Tenofovir alafenamide vs tenofovir disoproxil fumarate, each co-formulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials

[1]Bloch M, Sax P[2], Wohl D[3], Yin M[4], Post F[5], DeJesus E[6], Saag M[7], Pozniak A[8], Thompson M[9], Podzamczer D[10], Molina JM[11], Oka S[12], Koenig E[13], Trottier B[14], Andrade-Villanueva J[15], Crofoot G[16], Custodio J[17] Plummer A[17], Zhong L[17], Cao H[17], Martin H[17], Callebaut C[17], Cheng A[17], Fordyce M[17], McCallister S[17], for the GS-US-292-0104/0111 Study Team.

[1]Holdsworth House Medical Practice, [2]Brigham and Women's Hospital, [3]University of North Carolina, [4]Columbia University Medical Center, [5]King's College Hospital NHS Foundation Trust , [6]Orlando Immunology Center, [7]University of Alabama at Birmingham Medical Center, [8]Chelsea and Westminster NHS Trust, [9]AIDS Research Consortium of Atlanta, [10]Hospital Universitari de Bellvitge, [11]Saint-Louis Hospital and University of Paris, [12]International Medical Center of Japan, [13]Instituto Dominicano de Estudio-IDEV, [14]Clinique Medicale l'Actuel, [15]Centro Universitario de Ciencias de la Salud, [16]Crofoot Research, [17]Gilead Sciences.

Disclosure of Interest Statement

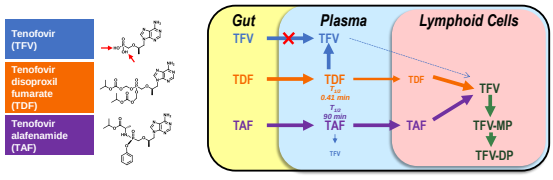
- Study 104 and 111 are Gilead Sciences sponsored Phase IIIb studies
- Dr. Bloch has received funding from, acted as an advisor for and/or participated in clinical research for: Gilead Sciences, Janssen, Merck, Bristol Myers Squibb ViiV Healthcare, Abbvie

Background

- Tenofovir disoproxil fumarate (TDF) is included in most recommended antiretroviral regimens, and although potent and generally well tolerated, has been associated with clinically significant renal and bone toxicity1-3
- Relative to TDF 300 mg, tenofovir alafenamide (TAF) 25 mg has 90% lower circulating plasma TFV, while maintaining high antiviral activity4
- In Phase 2, efficacy of elvitegravir, cobicistat, emtricitabine, and TAF (E/C/F/TAF) was comparable to E/C/F/TDF, and demonstrated significant improvements in renal and bone safety5
- We sought to confirm the efficacy of E/C/F/TAF in two fully powered clinical trials

1. DeJesus E, et al. Lancet 2012;379:2429-38; 2. Gallant JE, et al. J Infect Dis 2013;208:32-9; 3. Sax PE, et al. Lancet 2012;379:2439-48; 4. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-55; 5. Sax PE, et al. J Acquir Immune Defic Syndr 2014;67:52-8.

Tenofovir Alafenamide (TAF)
TAF is a Targeted Prodrug of TFV – Reduces Circulating TFV

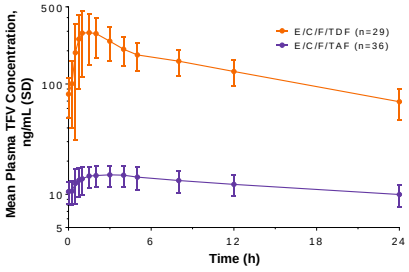


- TAF is more stable in plasma compared with TDF[1]
- Intact TAF transits directly into target cells where it is intracellularly activated to tenofovir disphosphate (TFV-DP)[1-3]
- TAF has 90% lower circulating plasma TFV levels compared to TDF 300mg[4-6]

1. Lee W et. Antimicr Agents Chemo 2005;49(5):1898-1906.
2. Birkus G et al. Antimicr Agents Chemo 2007;51(2):543-550.
3. Babusis D, et al. Mol Pharm 2013;10(2):459-66.
4. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5.
5. Sax P, et al. JAIDS 2014. 2014 Sep 1;67(1):52-8.
6. Sax P, et al. CROI 2015. Seattle, WA. #143LB

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Plasma TFV Concentrations

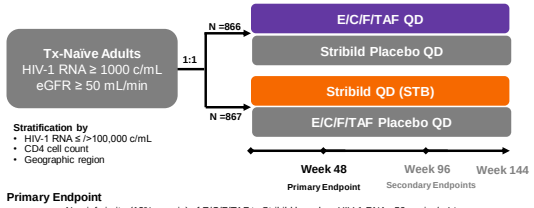


91% reduction in TFV plasma exposures with E/C/F/TAF

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Study Design

Two Phase 3, International, randomized, double-blind, active-controlled studies



Stratification by
- HIV-1 RNA ≤ />100,000 c/mL
- CD4 cell count
- Geographic region

Primary Endpoint
Non-inferiority (12% margin) of E/C/F/TAF to Stribild based on HIV-1 RNA <50 copies/mL* at Week 48 by FDA Snapshot analysis†

Secondary Endpoints
Efficacy, safety** and tolerability observed through Week 96, Week 144

*Taqman 2.0 assay
†Combined efficacy analysis was pre-specified. **SCr, proteinuria, hip and spine BMD were pre-specified week 48 safety endpoints.
Study 104 (North America, EU, Asia) and Study 111 (North America, EU, Latin America)

E/C/F/TAF: elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir alafenamide 10 mg
STB: elvitegravir 150 mg / cobicistat 150 mg / emtricitabine 200 mg / tenofovir DF 300 mg

ClinicalTrials.gov Identifier: NCT01780506 and NCT01797445

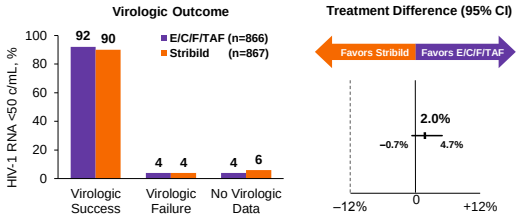
Studies 104 and 111: ART-Naïve Patients, Week 48 Combined Analysis

Baseline Characteristics

	E/C/F/TAF n=866	Stribild n=867
Age, median years	33	35
Sex		
Male, %	85	85
Female, %	15	15
Race/ethnicity		
Black or African descent, %	26	25
Hispanic/Latino ethnicity, %	19	19
Median HIV-1 RNA, $\log_{10}$ c/mL	4.58	4.58
HIV-1 RNA >100,000 c/mL, %	23	23
Median CD4 count, cells/µL	404	406
CD4 count <200, %	13	14
Median estimated GFR_{CG}, mL/min	117	114
Dipstick proteinuria (any grade), %	10	10

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

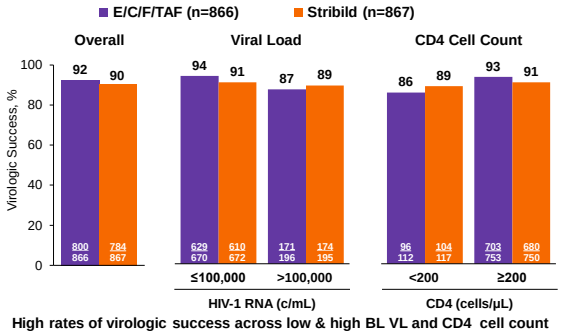
Virologic and Immunologic Outcomes at Week 48



- E/C/F/TAF was non-inferior to Stribild at Week 48 in each study
  - 93% E/C/F/TAF vs 92% Stribild (Study 104)
  - 92% E/C/F/TAF vs 89% Stribild (Study 111)
- Increase in CD4 count (cells/µL) at Week 48
  - E/C/F/TAF: +211 vs Stribild: +181 (*P*=0.024)

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

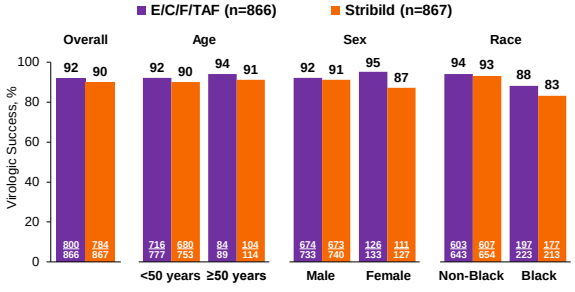
Efficacy by Baseline HIV-1 RNA and CD4 Cell Count



High rates of virologic success across low & high BL VL and CD4 cell count

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Efficacy by Age, Sex, and Race Subgroups



High rates of virologic success across age, sex, and race subgroups

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Emergent Resistance Through Week 48

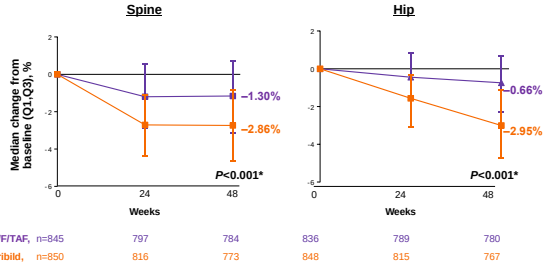
		E/C/F/TAF n=866	Stribild n=867
Adults analyzed for resistance*, n (%)		**16 (1.8)**	**19 (2.2)**
Primary Genotypic Resistance	**n (%)**	**7 (0.8)**	**5 (0.6)**
NRTI Resistance	**n**	**7**	**5**
	M184V/I	6	3
	M184V/I + K65R	1	2
INSTI Resistance	**n**	**5**	**3**
		T66A (1), E92Q (2), N155H (1), Q148+T66I/A (1)	E92Q (1), Q148R (1), Q148R+E92Q (1)

*With 2 consecutive HIV-1 RNA ≥50 c/mL after first achieving <50 c/mL and the second ≥400 c/mL; or had ≥400 c/mL at Week 48 or last study visit.

0.8% developed treatment emergent resistance on E/C/F/TAF

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Changes in Spine and Hip BMD Through Week 48

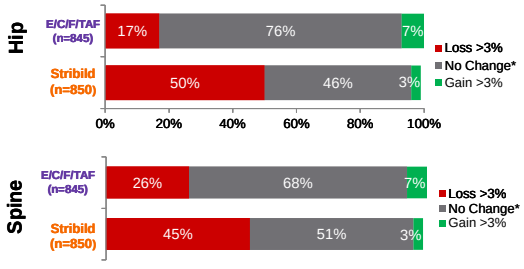


Significantly less decrease in spine and hip BMD in the E/C/F/TAF group at Week 48

*Comparison of E/C/F/TAF vs Stribild at Week 48

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

BMD Categorical Changes at Week 48

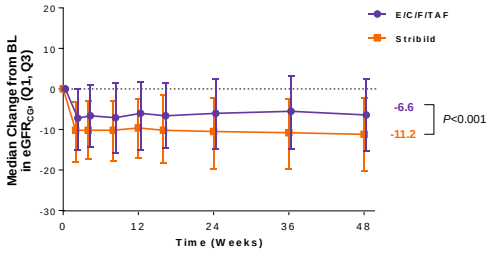


*No Change = -3% to +3%

13

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Changes in eGFR (Cockcroft-Gault) Through Week 48



Less GFR decline with E/C/F/TAF compared to Stribild (p<0.001)

Pattern of early decline (2 wks) then stable eGFR is consistent with cobicistat inhibition of tubular secretion of creatinine

14

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Renal Adverse Events and Tubulopathy

		E/C/F/TAF n=866	Stribild n=867
Events n (%)	**Renal adverse events**	0	4 (0.5)*
	Tubulopathy/Fanconi syndrome	**0**	**0**
Laboratory Abnormalities n (%)	**Subclinical tubulopathy†**	0	1 (0.1)
	Serum creatinine (≥0.4 mg/dL increase)	0	0
	Hypophosphatemia (≥1 grade increase)	3 (0.3)	4 (0.5)
	Normoglycemic glycosuria (≥1 grade increase urine glucose; serum glucose ≤100 mg/dL)	0	2 (0.2)
	Proteinuria (≥2 grade increase)	2 (0.2)	2 (0.2)

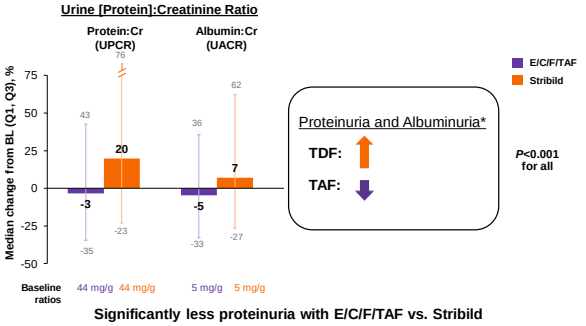
*Renal failure (2), decreased GFR (1), nephropathy (1)
†Confirmed abnormality in any 2 categories at 2 consecutive post-baseline visits

No renal adverse events in E/C/F/TAF arm

15

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Changes (%) in Quantitative Proteinuria at Week 48



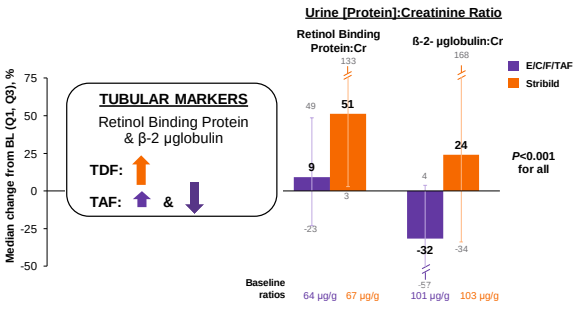
Significantly less proteinuria with E/C/F/TAF vs. Stribild

*94% of filtered albumin is reabsorbed in the tubules (Tojo A and Kinugasa S. Mechanism of glomerular albumin filtration and tubular reabsorption. Int J Nephrol 2012:9)

16

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Changes (%) in Quantitative Proteinuria at Week 48

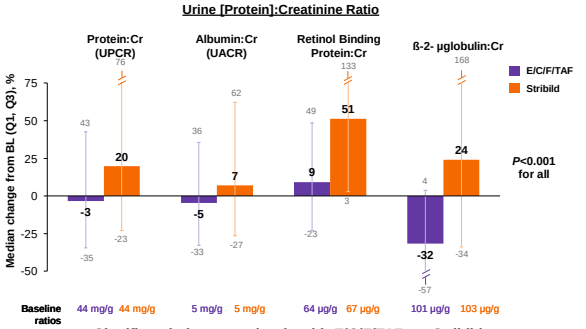


Significantly less proteinuria with E/C/F/TAF vs. Stribild

17

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Changes (%) in Quantitative Proteinuria at Week 48

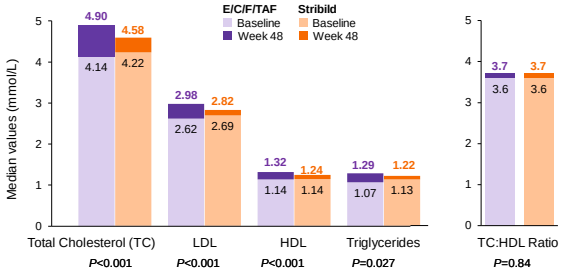


Significantly less proteinuria with E/C/F/TAF vs. Stribild

18

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Fasting Lipids at Week 48



Subjects initiating lipid-modifying medications: 3.6% E/C/F/TAF vs 2.9% Stribild (*P*=0.42).

Changes in TC, LDL, TG were balanced by changes in HDL on TAF compared to TDF with no difference between the arms on the TC:HDL ratio

19

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Safety Summary Through Week 48

%	E/C/F/TAF n=866	Stribild n=867
Adverse Events (AE)	90	90
Any drug-related AE	40	42
Grade 3 or 4 AE	8	9
Drug-related Grade 3 or 4 AE	1	1
Serious AE	8	7
Drug-related serious AE	0.3	0.2
AE-related discontinuation, % (n)	0.9 (8)	1.5 (13)
Deaths	0.2*	0.3†

*Stroke (1), alcohol intoxication (1).
†Alcohol and drug intoxication (1), myocardial infarction (2).

Discontinuations due to AEs occurred in 0.9% in the E/C/F/TAF arm

20

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Common Adverse Events (≥5%) Through Week 48

Adverse event (all grades), %	E/C/F/TAF n=866	Stribild n=867
Diarrhea	17	19
Nausea	15	17
Headache	14	13
Upper respiratory tract infection	11	13
Nasopharyngitis	9	9
Fatigue	8	8
Cough	8	7
Vomiting	7	6
Arthralgia	7	5
Back pain	7	7
Insomnia	7	6
Rash	6	5
Pyrexia	5	5
Dizziness	5	4

Rates and types of AEs were similar between both arms. No new safety findings.

21

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Grade 3 or 4 Lab Abnormalities

	E/C/F/TAF n=866	Stribild n=867
Grade 3 or 4 lab abnormalities* ,%	20	20
Creatine kinase elevation	7	6
LDL elevation (fasting)	5	2
Hypercholesterolemia (fasting)	2	1
Hematuria (quantitative)	2	2
AST elevation	2	2
Serum amylase elevation	2	3
Neutropenia (<1000 cells/µL)	2	2
ALT elevation	1	1

*≥1% on E/C/F/TAF arm

Similar types and rates of grade 3 or 4 lab abnormalities

22

Studies 104 and 111: ART-Naïve Adults, Week 48 Combined Analysis

Conclusions

Phase 3 E/C/F/TAF studies of 1,733 ART-naïve patients demonstrated

- **Non-inferior efficacy** to Stribild at W48 with **high and similar virologic success rates** across studies (93% Study 104 & 92% Study 111) and subgroups (HIV-1 RNA, CD4 count, age, sex, and race)
- **Low virologic failure rates with <1% resistance** in both arms
- **Well tolerated with low discontinuations due to AEs** (0.9% E/C/F/TAF vs 1.6% Stribild) and similar common AEs to Stribild
- Detailed protocol-specified **renal and bone endpoints confirmed the favorable safety and tolerability profile** of TAF vs. TDF
  - No discontinuations due to renal AEs
  - Significantly less eGFR decline and less proteinuria, albuminuria, and tubular proteinuria
  - Significantly less impact on spine and hip BMD

23