A Daily Single-Tablet Regimen of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed Adults Living With HIV and End-stage Renal Disease on Chronic Hemodialysis

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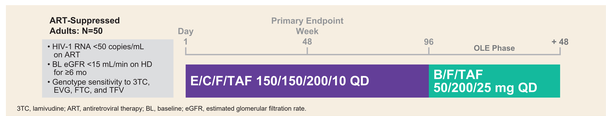
Introduction

- Treatment for people living with HIV (PLWH) and end-stage renal disease (ESRD) on hemodialysis (HD) has previously required complex dose-adjusted regimens
- We previously evaluated elvitegravir (EVG)/cobicistat/emtricitabine (FTC)/tenofovir (TFV) alafenamide (TAF; E/C/F/TAF) daily, and established this treatment as effective and safe, showing that daily TAF resulted in lower plasma TFV exposure than a historical comparison of once-weekly TFV disoproxil fumarate in patients with ESRD on HD[1,2]
- The single-tablet regimen (STR) bictegravir (BIC)/FTC/TAF (B/F/TAF) is a US DHHS, EACS, and IAS-USA guidelines-recommended regimen,[3-5] with demonstrated safety and efficacy, a high barrier to resistance, and limited potential drug-drug interactions
- Based on B/F/TAF Phase 3 data and FDA approval, the protocol was amended to allow eligible US participants to enroll in an open-label extension (OLE) with B/F/TAF

Objectives

- To assess the safety and tolerability of the B/F/TAF STR in PLWH with ESRD on chronic HD at Week 48

Methods



3TC, lamivudine; ART, antiretroviral therapy; BL, baseline; eGFR, estimated glomerular filtration rate.

- Phase 3B, open-label, multicenter, single-arm study in North America and Europe (GS-US-292-1825 [NCT02600819])
  - Protocol amended in 2018 for US participants after B/F/TAF regulatory approval by FDA
  - Participants who remained in study follow-up switched to B/F/TAF in the OLE phase
- Assessments during B/F/TAF OLE:
  - Safety: adverse events (AEs) and laboratory abnormalities
  - Efficacy: proportion of participants with virologic suppression (HIV RNA <50 copies/mL) by missing = excluded (M=E)
  - Pharmacokinetics (PK): sampling at Weeks 4, 24, and 48

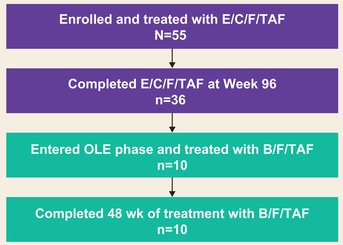
Results

Baseline Characteristics

		B/F/TAF: n=10
Median age at B/F/TAF start, y (range)		55 (34–63)
Sex at birth, n (%)	Male	8 (80)
	Female	2 (20)
Race, n (%)	Black	9 (90)
	White	1 (10)
HIV-1 RNA <50 copies/mL at B/F/TAF start, n (%)		10 (100)
Median CD4 cells/μL at B/F/TAF start (IQR)		563 (451, 705)
Mode of infection, n (%)*	Heterosexual sex	6 (60)
	Homosexual sex	3 (30)
	Injection drug use	1 (10)
	Unknown	1 (10)
Hepatitis C virus antibody positive, n (%)		5 (50)
Median $eGFR_{CG}$ at B/F/TAF start, mL/min (IQR)†		11.6 (7.8, 14.6)
Median years on HD (range)		4 (2–16)
Medical history, n (%)	Diabetes	4 (40)
	Hypertension	10 (100)
	Cardiovascular disease	6 (60)
	Hyperlipidemia	3 (30)

*Participants may fit >1 category; †Timing of blood draw variable. CD4, cluster of differentiation-4; $eGFR_{CG}$, eGFR by Cockcroft-Gault equation; IQR, interquartile range.

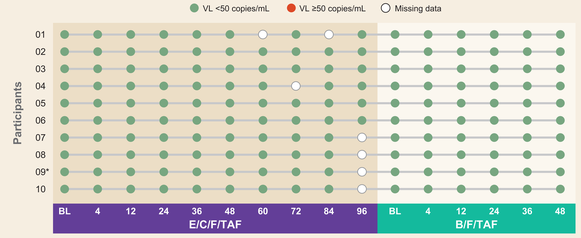
Participant Disposition*



*15 participants were on study at time of amendment to add B/F/TAF.

- Median duration of exposure to B/F/TAF: 48 wk (range 47–52)

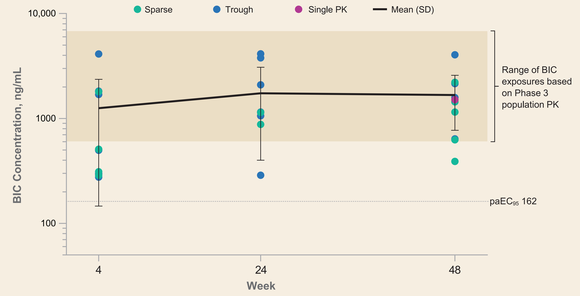
Virologic Outcomes



*1 participant continued E/C/F/TAF through Week 108 and switched to B/F/TAF at Week 120. VL, viral load.

- At 48 wk after switching to B/F/TAF, all 10 participants (100%) maintained virologic suppression (HIV RNA <50 copies/mL) by M=E
- For the 10 participants who switched to B/F/TAF, median (IQR) CD4 count at BL was 563 (451, 705) cells/μL and median change from BL at Week 48 (n=9) was -121 (IQR -144, -21) cells/μL
- No participants met the criteria for resistance testing

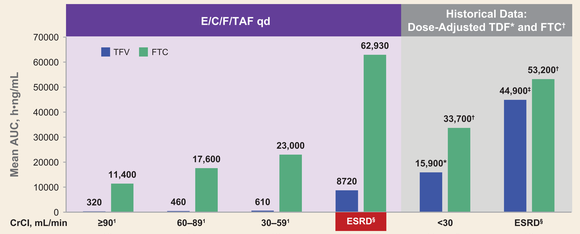
Pharmacokinetic Results: BIC Concentrations



$paEC_{95}$, protein-adjusted 95% effective concentration; SD, standard deviation.

- In participants with available data, mean BIC concentrations were lower vs PLWH not on HD
- BIC trough concentrations remained 4- to 7-fold higher than the BIC established $paEC_{95}$ of 162 ng/mL against wild-type virus from Phase 3 study results

TFV and FTC Exposures Among Adults With Various Degrees of Renal Impairment[1]



*Recommended dose: 300 mg q72–96h in patients with creatinine clearance (CrCl) 10–29 mL/min or q7d in patients on HD; †Recommended dose is 200 mg q72h in patients with CrCl 15–29 mL/min or q96h in patients on HD; ‡Study GS-01-919; §Requiring HD; current study, E/C/F/TAF phase. AUC, area under curve.

- FTC and TFV exposures were higher in individuals on HD vs historical data from E/C/F/TAF in HIV-1–infected adults with normal renal function or mild–moderate renal impairment
- TFV exposures were substantially lower than historical data with TDF dosed once weekly in HD
- FTC exposures were similar to historical data with FTC in HD

Pharmacokinetic Results: TAF and FTC[1]

Mean, h·ng/mL (%CV)		E/C/F/TAF n	ESRD	n	Normal Renal Function
FTC	AUC_{tau}	11	62,900 (48)	18*	11,400 (12)
TAF	AUC_{last}	12	232 (53)	18*	230 (47)
TFV	AUC_{tau}	10	8720 (39)	18*	320 (15)

*From intensive PK analysis in a Phase 2 trial (Study 102) in HIV-infected adults.† AUC_{last}, AUC up to last measurable concentration; AUC_{tau}, AUC over dosing interval; CV, coefficient of variation.

- Exposures of TAF, hepatically metabolized, were consistent with the ranges of historical data in PLWH with normal renal function[8]
- As expected, exposures of the renally eliminated metabolite TFV were higher than with TAF in normal renal function
- Exposures of FTC, also renally eliminated, were higher than in individuals with normal renal function, but safety profile was similar

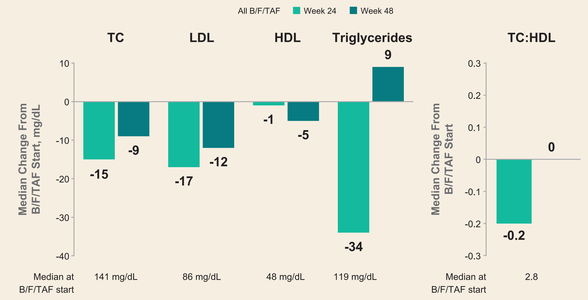
Summary of Adverse Events and Laboratory Abnormalities

n (%)	B/F/TAF: n=10
Any AE	10 (100)
AEs occurring in >1 participant	
Dyspnea	2 (20)
Hypertension	2 (20)
Grade 3 or 4 AE*	1 (10)
Study drug-related AE	1 (10)
Serious AE†	3 (30)
AE leading to study drug discontinuation	0
Death	0
Any Grade 3 or 4 laboratory abnormality	5 (50)
Increased amylase	2 (20)
Increased creatinine	1 (10)
Increased GGT	1 (10)
Serum potassium (hyperkalemia)	1 (10)

*1 participant had multiple Grade 3 AEs of congestive cardiac failure, abdominal wall hematoma, pneumonia, respiratory syncytial viral pneumonia, vascular access site hemorrhage, cervical spinal stenosis, spinal stenosis, hypertensive emergency, and hypertensive urgency; none were treatment related; †Serious AEs included tendon rupture, hyperkalemia, and dyspnea (n=1); angina pectoris, acute myocardial infarction, and skin ulcer (n=1); and vascular access site hemorrhage, pneumonia, respiratory syncytial viral pneumonia, hypertensive urgency, abdominal wall hematoma, cervical spinal stenosis, hypertensive emergency, congestive cardiac failure, and spinal stenosis (n=1); none were treatment related. GGT, γ-glutamyltransferase.

- Most AEs were Grade 1 or 2 in severity
- 1 participant had study-drug related AEs of Grade 2 nausea and Grade 1 malaise
- No Grade ≥3 or serious AEs were considered related to study drug

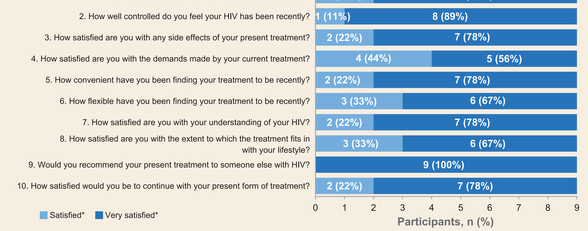
Median Changes From Baseline in Fasting Lipid Parameters



HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.

- There were no clinically relevant changes from BL in median fasting lipid parameters at Weeks 24 and 48 after switching to B/F/TAF
- No participants initiated lipid-modifying agents after switch

HIV Treatment Satisfaction and Adherence at Week 48 After Switch to B/F/TAF



*For 2: well controlled and very well controlled; 5: convenient and very convenient; 6: flexible and very flexible; 9: "Yes, I would recommend the treatment" and "Yes, I would definitely recommend the treatment."

- Median adherence through Week 48 was 89% (IQR 84, 98) as measured by pill count

Conclusions

- In this 1st evaluation of the once-daily B/F/TAF STR in PLWH with ESRD on HD, all participants maintained virologic suppression
- B/F/TAF had a favorable safety and tolerability profile over 48 wk, with no discontinuations
- In participants with evaluable data, mean BIC concentrations were lower compared with PLWH not on HD
- BIC trough concentrations remained 4- to 7-fold higher than the BIC established $paEC_{95}$ against wild-type virus from Phase 3 study results
- Simplification to the B/F/TAF STR offers an effective, safe, and convenient once-daily option for PLWH on HD, who often have complicated HIV dosing schedules, multiple comorbidities, and a high pill burden

References: **1.** Eron JJ Jr, et al. CROI 2018, poster P-N02; **2.** Eron JJ Jr, et al. Lancet HIV 2018;S2352-3018(18)30296-0; **3.** Clinical Info HIV.gov. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV; 7/10/19; **4.** EACS Guidelines Version 10.1 October 2020; **5.** Saag MS, et al. JAMA 2018;320:379-96; **6.** Viread [package insert]. Foster City, CA: Gilead Sciences, Inc., 4/17; **7.** Emtriva [package insert]. Foster City, CA: Gilead Sciences, Inc., 4/17; **8.** Genvoya [package insert]. Foster City, CA: Gilead Sciences, Inc., 12/18. **Acknowledgments:** We extend our thanks to the participants, their families, and all study investigators and staff who participated in this OLE phase: DM Asmuth, E DeJesus, JJ Eron Jr, MS McKellar, OO Osiyemi, M Ramgopal, J Slim, AM Wilkin. This study was funded by Gilead Sciences, Inc.