795

Safety of Tenofovir Alafenamide in Renal Impairment

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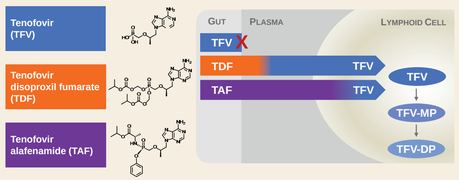
Introduction

Tenofovir Alafenamide (TAF, GS-7340) Novel Prodrug of Tenofovir



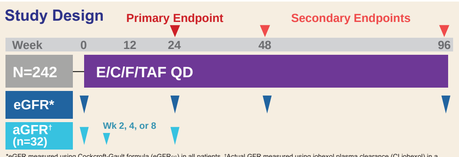
- TDF has been associated with clinically significant renal and bone toxicity[1-3]
  - Patients with estimated glomerular filtration rate (eGFR) <50 mL/min require dose adjustment
  - Patients with eGFR <70 mL/min should not initiate Stribild (elvitegravir/cobicistat/emtricitabine/TDF [E/C/F/TDF])
- Relative to TDF 300 mg, TAF at an equivalent dose of 25 mg has 90% lower circulating plasma TFV, while maintaining high antiviral activity[4]
- In 2 randomized, blinded, Phase 3 studies of E/C/F/TAF vs E/C/F/TDF:
  - E/C/F/TAF was noninferior to E/C/F/TDF[5]
  - Prespecified renal and bone safety endpoints (hip bone mineral density [BMD], spine BMD, serum creatinine, and treatment-emergent proteinuria) showed significantly less change with E/C/F/TAF compared with E/C/F/TDF[6]

Objective

- To evaluate safety and efficacy of a once-daily, single-tablet regimen of E/C/F/TAF in HIV-1–infected patients with mild to moderate renal impairment

Methods

Study Design



*eGFR measured using Cockcroft-Gault formula ($eGFR_{CG}$) in all patients. †Actual GFR measured using iohexol plasma clearance (CLiohexol) in a subset of patients at 3 time points: baseline; Week 2, 4, or 8; and Week 24.

- Phase 3, 96-week, multicenter, open-label study (NCT01818596)
- Virologically suppressed adults with stable $eGFR_{CG}$ (30–69 mL/min) switched from TDF- or non-TDF–containing regimens to open-label E/C/F/TAF
- Week 48 efficacy and safety data are described, including tests of renal function and BMD
- Actual GFR (aGFR) was assessed with iohexol clearance in a patient subset

Key Inclusion Criteria

- CD4 cell count ≥50 cells/μL
- No chronic hepatitis B or C virus infection
- HIV-1 RNA
  - HIV-suppressed patients: <50 copies/mL for ≥6 months

Primary Safety Endpoint

- Change from baseline in eGFR at Week 24

Secondary Endpoints

- Efficacy, safety, and tolerability through Week 48
- Proportion of patients with HIV-1 RNA <50 copies/mL

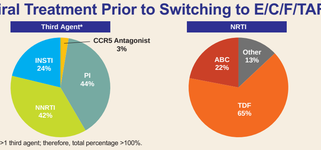
Results

Baseline Characteristics

	Baseline eGFR		
	<50 mL/min n=80	≥50 mL/min n=162	Total N=242
Median age, year (IQR)	59 (52, 66)	58 (51, 64)	58 (52, 65)
Age ≥65 years, n (%)	25 (31)	38 (23)	63 (26)
Female, n (%)	21 (26)	29 (18)	50 (21)
Black or African descent, %	18	19	18
HIV-1 RNA <50 copies/mL, %	98	98	98
Median CD4 count, cells/μL	622	635	632
Pre-switch TDF use, %	58	69	65
Hypertension, %	50	34	39
Diabetes, %	15	13	14
Median $eGFR_{CG}$, mL/min	43	60	56
Median $eGFR_{CKD\text{-}EPI,\ creatinine}$, mL/min/1.73 m²*	45	58	54
Median $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$, mL/min/1.73 m²†	57	77	70
Dipstick proteinuria Grade 1 or 2, %‡	44	27	33
Clinically significant proteinuria, %§	56	35	42
Clinically significant albuminuria, %¶	64	42	49

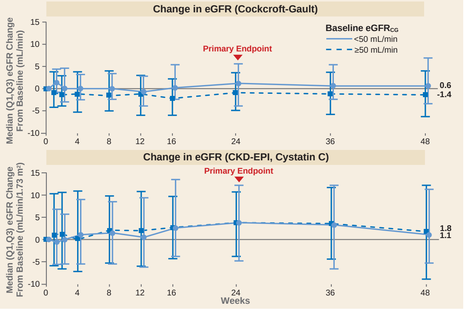
*Chronic Kidney Disease Epidemiology Collaboration equation for eGFR using serum creatinine ($eGFR_{CKD\text{-}EPI,\ creatinine}$); adjusted for age, sex, and race. †CKD-EPI equation for eGFR using cystatin C ($eGFR_{CKD\text{-}EPI,\ cystatin\ C}$); adjusted for age and sex. ‡Grade 1 (1+ on dipstick), Grade 2 (2–3+ on dipstick). §Urine protein:creatinine (UPCR) >200 mg/g. ¶Urine albumin:creatinine (UACR, ie, microalbuminuria) ≥30 mg/g.

Antiretroviral Treatment Prior to Switching to E/C/F/TAF



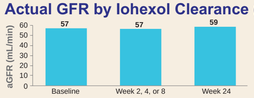
*Some regimens included >1 third agent; therefore, total percentage >100%.

Change in eGFR From Baseline to Week 48



- At Week 24, median (Q1, Q3) change from baseline in $eGFR_{CG}$ was -0.4 (-4.8, 4.5) mL/min, and in $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$ was 3.8 (-4.8, 11.2) mL/min/1.73 m²
- There was no significant change in $eGFR_{CG}$ or $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$ to Week 48

Actual GFR by Iohexol Clearance (n=32)

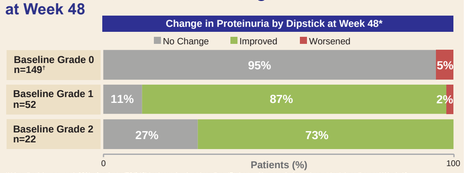


	GLSM Ratio (%)	90% CI
Week 2, 4,or 8 vs baseline	99	94,104
Week 24 vs baseline	103	97, 109

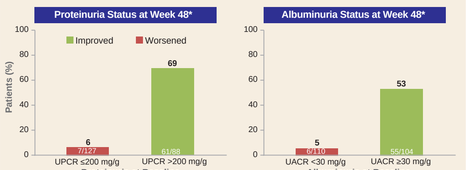
CI, confidence interval; GLSM, geometric least squares mean.

- Predefined lack of alteration boundary defined as 80–125% (GLSM)
- Actual GFR was not affected over 24 weeks of treatment
  - No difference between patients with baseline $eGFR_{CG}$ <50 vs ≥50 mL/min, or between those taking TDF vs non-TDF–containing regimens before switching to E/C/F/TAF (data not shown)

Proteinuria and Albuminuria Change From Baseline at Week 48



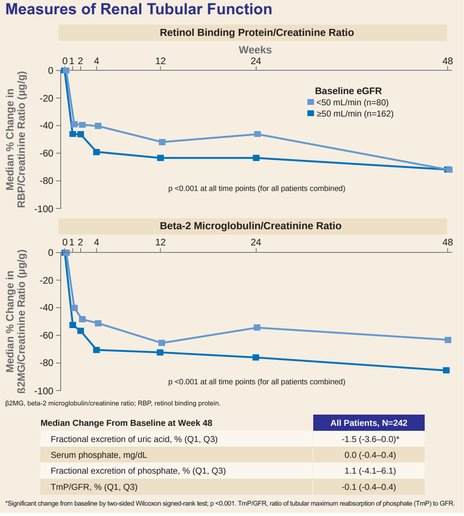
*Urine dipstick was used; 33% of patients (79/242) had proteinuria at baseline. †Patients with non-missing values at both baseline and Week 48. Improved proteinuria = baseline Grade 1 → Grade 0, or baseline Grade 2 → Grade 1 or 0. Worsened proteinuria = baseline Grade 0 → Grade 1, or baseline Grade 1 → Grade 2.



*Significant median decrease from baseline to Week 48 by two-sided Wilcoxon signed-rank test (p <0.001). Improved = change from clinically significant UPCR (>200 mg/g) or UACR (≥30 mg/g) to nonsignificant UPCR or UACR. Worsened = change from nonsignificant to clinically significant UPCR or UACR. UACR, urine albumin:creatinine ratio; UPCR, urine protein:creatinine ratio.

- Most patients with dipstick proteinuria at baseline improved
- Decreased prevalence of clinically significant proteinuria and albuminuria

Measures of Renal Tubular Function



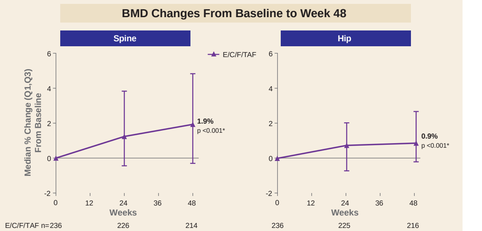
β2MG, beta-2 microglobulin/creatinine ratio; RBP, retinol binding protein.

Median Change From Baseline at Week 48	All Patients, N=242
Fractional excretion of uric acid, % (Q1, Q3)	-1.5 (-3.6–0.0)*
Serum phosphate, mg/dL	0.0 (-0.4–0.4)
Fractional excretion of phosphate, % (Q1, Q3)	1.1 (-4.1–6.1)
TmP/GFR, % (Q1, Q3)	-0.1 (-0.4–0.4)

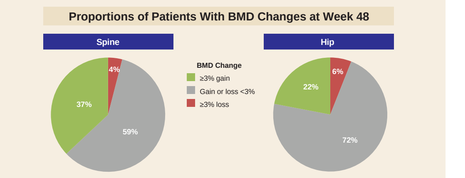
*Significant change from baseline by two-sided Wilcoxon signed-rank test; p <0.001. TmP/GFR, ratio of tubular maximum reabsorption of phosphate (TmP) to GFR.

- Significant improvements in urine retinol binding protein/creatinine ratio, beta-2 microglobulin/creatinine ratio, and fractional excretion of uric acid levels were observed (p <0.001 for all)

Change in Spine and Hip Bone Mineral Density

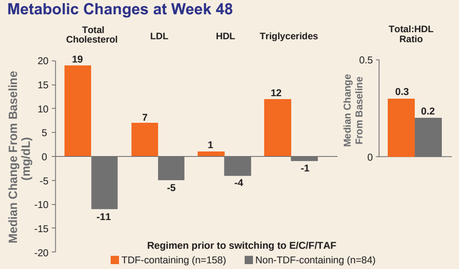


*Two-sided Wilcoxon signed-rank test.



- Median percentage changes (Q1, Q3) in hip and spine BMD from baseline to Week 48 were 0.9% (-0.3, 2.7) and 1.9% (-0.3, 4.3), respectively

Metabolic Changes at Week 48



- Fasting lipid levels decreased in patients who used non-TDF-containing regimens prior to switching to E/C/F/TAF, whereas levels increased in those using TDF-containing regimens prior to switching to E/C/F/TAF

Virologic Outcomes at Week 48 (by FDA snapshot)

- 92% (222 patients) maintained HIV-1 viral load <50 copies/mL at Week 48
- 7% (17 patients), virologic data not available
  - 7 patients discontinued due to adverse events (AEs) by Week 48: renal failure (see next column), diarrhea, choking, fatigue/pain/pruritus, arthralgia/joint swelling, sleep disorder, bladder cancer
    - After Week 48, 1 patient died (cardiopulmonary arrest), and 1 additional patient discontinued due to chronic renal failure (see next column)
  - 7 patients discontinued due to other reasons and last available HIV-1 RNA <50 copies/mL (lost to follow-up, noncompliance, protocol violation, or discontinued by sponsor)
  - 3 patients had missing data in the Week 48 window
- 1% (3 patients) had virologic failure
  - 2 patients showed resistance
    - 1 patient with HIV-1 RNA <50 copies/mL on E/C/F/TAF prior to switching to new regimen
    - 1 patient with HIV-1 RNA <400 copies/mL on E/C/F/TAF; NRTI and PI resistance identical to pre-study historical genotype
  - 1 patient took additional antiretrovirals (rilpivirine/emtricitabine/TDF) through Day 67 (protocol violation)
    - Now on E/C/F/TAF alone with HIV-1 RNA <50 copies/mL through Week 48

Adverse Events in ≥5% of Patients to Week 48

Patients, %	Baseline eGFR		
	<50 mL/min n=80	≥50 mL/min n=162	Total N=242
Diarrhea	13	11	11
Arthralgia	8	10	9
Upper respiratory tract infection	3	12	9
Bronchitis	9	8	8
Osteopenia*	11	7	8
Nausea	6	9	8
Headache	3	9	7
Pain in extremity	5	8	7
Back pain	4	8	7
Dizziness	10	4	6
Fatigue	5	6	6
Renal cyst	6	6	6
Cough	5	6	6

*Of 19 patients, 16 had osteopenia at baseline; the other 3 had an AE of osteopenia reported within 12 days after switching to E/C/F/TAF.

- Diarrhea (9%), arthralgia (8%), and bronchitis (8%) were the most commonly reported adverse events
- Adverse events, grades, and frequencies were similar in patients with baseline eGFR <50 vs ≥50 mL/min
- 2 patients (0.8%) discontinued study drug for decreased GFR by $eGFR_{CG}$ and $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$, neither with evidence of renal tubulopathy
  - 1 patient with labile hypertension assessed as possibly related to concomitant ramipril and valsartan use and study drug
  - 1 patient assessed as likely related to progression of hypertension-related chronic kidney disease and not related to study drug
- No patient developed proximal renal tubulopathy or Fanconi syndrome

Conclusions

- This is the first study of a single-tablet antiretroviral regimen without dose adjustment in patients with eGFR between 30 and 69 mL/min, in which the median baseline age is 58 years
- 92% of patients maintained HIV-1 RNA <50 copies/mL at Week 48
- Switching to E/C/F/TAF was associated with no change in actual GFR, reductions in proteinuria and markers of proximal renal tubular function, and improvements in hip and spine bone mineral density
- Adverse events, grades, and frequencies were similar in patients with baseline eGFR <50 vs ≥50 mL/min
- These 48-week data support the virologic efficacy and renal and bone safety of once daily, single-tablet E/C/F/TAF therapy for patients with HIV and mild to moderate renal impairment (eGFR 30–69 mL/min)

References

1. DeJesus E, et al. Lancet 2012;379:2429-38; **2.** Gallant JE, et al. J Infect Dis 2013;208:32-39; **3.** Sax PE, et al. Lancet 2012;379:2439-48; **4.** Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5; **5.** Wohl D, et al. CROI 2015, Abstract 113LB; **6.** Sax P, et al. CROI 2015, Abstract 143LB.

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Study Investigators

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