ARV Therapies and Therapeutic Strategies

REPORTING ON CROI 2015

Comprehensive Expert Review and Discussion of Key Presentations

An Independent CME Activity Jointly Provided by Postgraduate Institute for Medicine and ViralEd, Inc.
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Renal and Bone Safety of Tenofovir Alafenamide vs. Tenofovir Disoproxil Fumarate

Combined Safety Results of Studies GS-US-292-0104 and GS-US-292-0111

Paul Sax[1], Michael Saag[2], Michael Yin[3], Frank Post[4], Shinichi Oka[5], Ellen Koenig[6], Benoit Trottier[7], Jaime Andrade-Villanueva[8], Huyen Cao[9], Marshall Fordyce[9]

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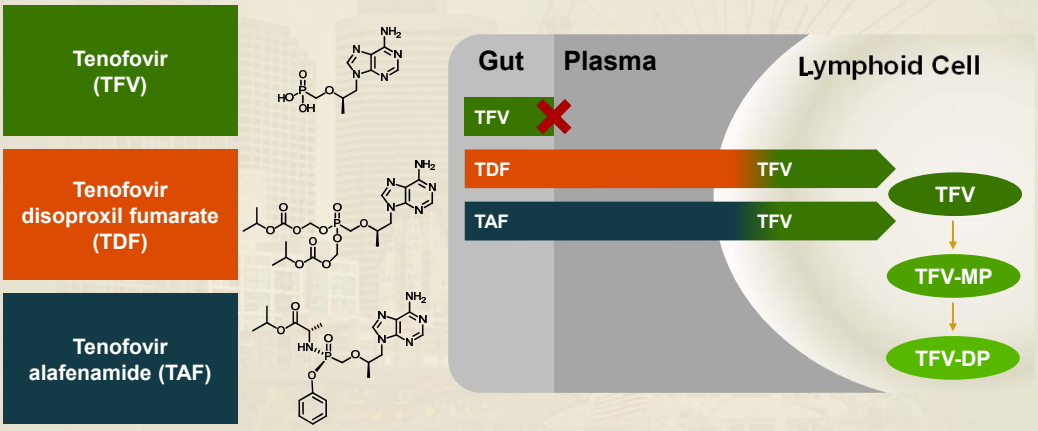
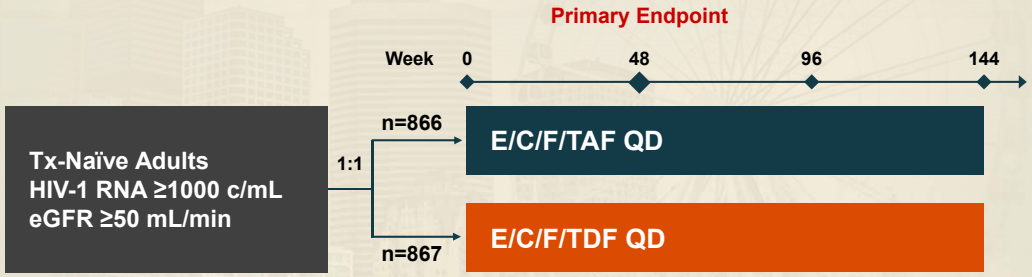
Abstract 143LB

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



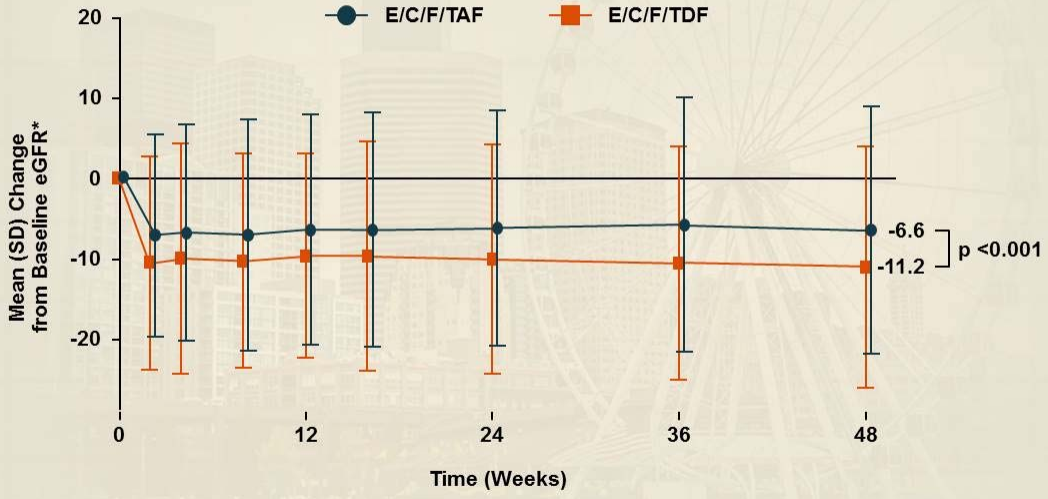
Wohl D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 113LB.

TAF vs TDF: Study Design



Wohl D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 113LB.

Change in eGFR (Cockcroft-Gault) Studies 104 and 111: Week 48 Combined Analysis



*Cockroft-Gault (mL/min).

Wohl D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 113LB.

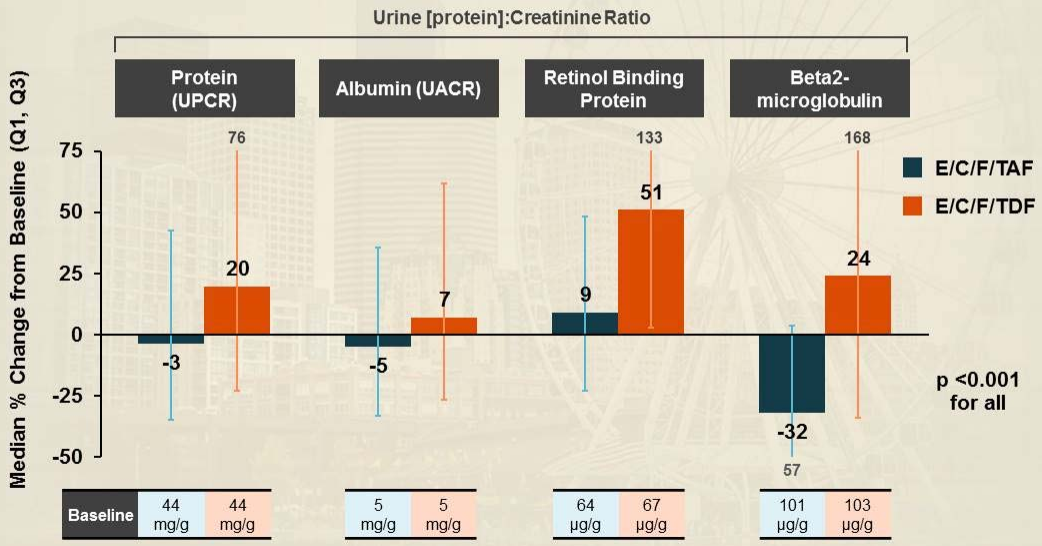
Renal Adverse Events and Tubulopathy Studies 104 and 111: Week 48 Combined Analysis

	n (%)	E/C/F/TAF n=866	E/C/F/TDF n=867
Events	Renal adverse events leading to discontinuation	0	4 (0.5)*
	Tubulopathy/Fanconi syndrome	0	0
	Subclinical tubulopathy†	0	1 (0.1)
Laboratory Abnormalities	Serum creatinine (≥0.4 mg/dL increase)	0	0
	Hypophosphatemia (≥1 grade decrease)	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.

Wohl D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 113LB.

Changes in Quantitative Proteinuria at Week 48 Studies 104 and 111: Week 48 Combined Analysis



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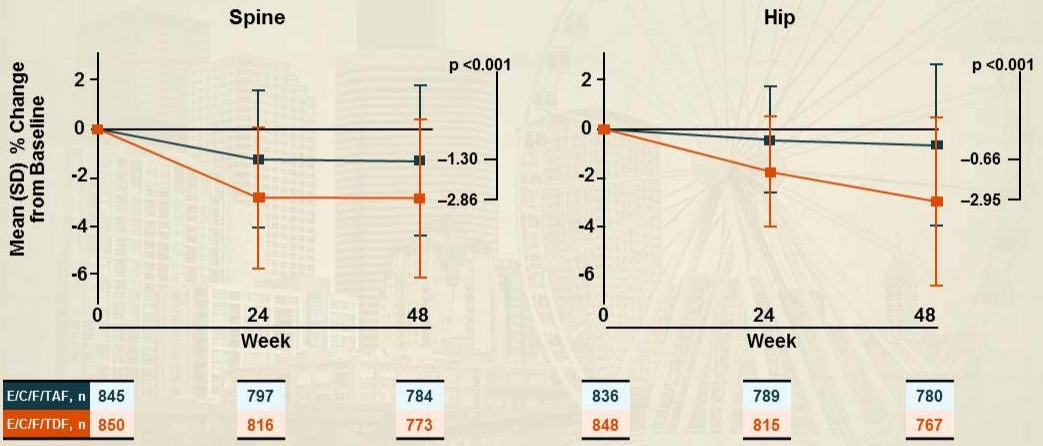
TAF vs TDF: Changes in Spine and Hip BMD



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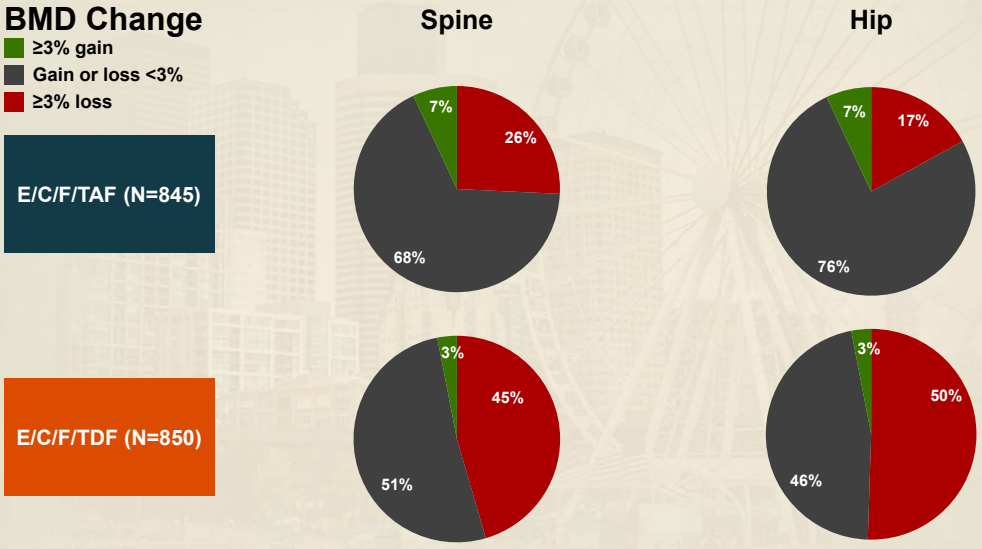
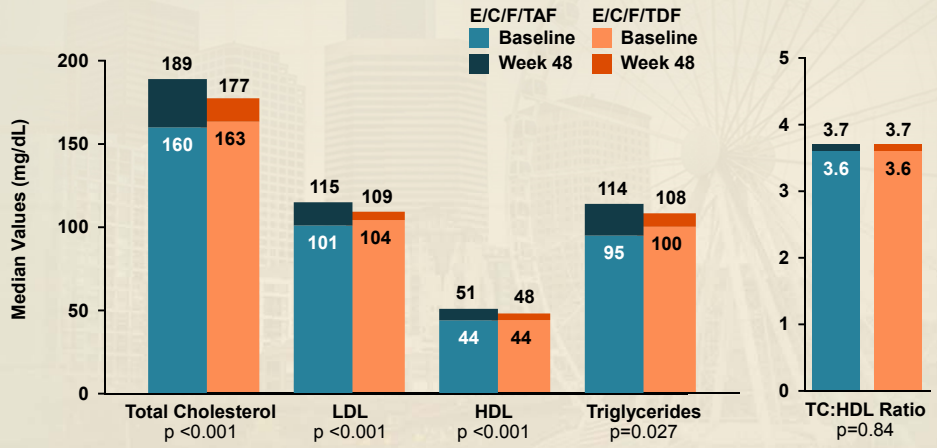
TAF vs TDF: BMD Categorical Changes



Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.

TAF vs TDF: Fasting Lipids



Patients initiating lipid-modifying medications: 3.6% E/C/F/TAF vs 2.9% E/C/F/TDF (p=0.42)

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.

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Safety of Tenofovir Alafenamide in Renal Impairment

Anton Pozniak[1], Jose Arribas[2], Samir K. Gupta[3], Frank A. Post[4], Anchalee Avihingsanon[5], Gordon Crofoot[6], Kenneth Lichtenstein[7], Moti Ramgopal[8], Ploenchan Chetchotisakd[9], Marshall W. Fordyce[10]

[1]Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; [2]Hospital Universitario La Paz, Madrid, Spain; [3]Indiana University School of Medicine, Indianapolis, IN; [4]King's College Hospital NHS Foundation Trust, London, UK; [5]HIV-NAT, Thai Red Cross AIDS Research Center and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [6]Crofoot Research, Houston, TX; [7]National Jewish Health, Denver, CO; [8]Midway Research Center, Ft. Pierce, FL; [9]Khon Kaen University, Thailand; [10]Gilead Sciences, Inc., Foster City, CA

Poster 795

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**

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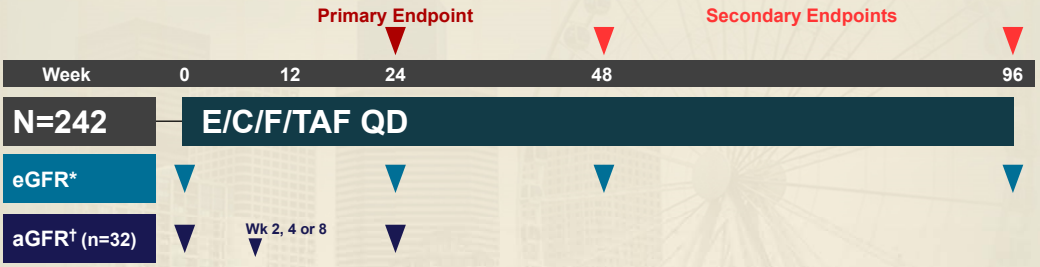
Study Design



- **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**

*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.

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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 m^2 *	45	58	54
Median $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$, mL/min/1.73 m^2 †	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 (eGFRCKD-EPI, creatinine); adjusted for age, sex, and race.
†CKD-EPI equation for eGFR using cystatin C (eGFRCKD-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.

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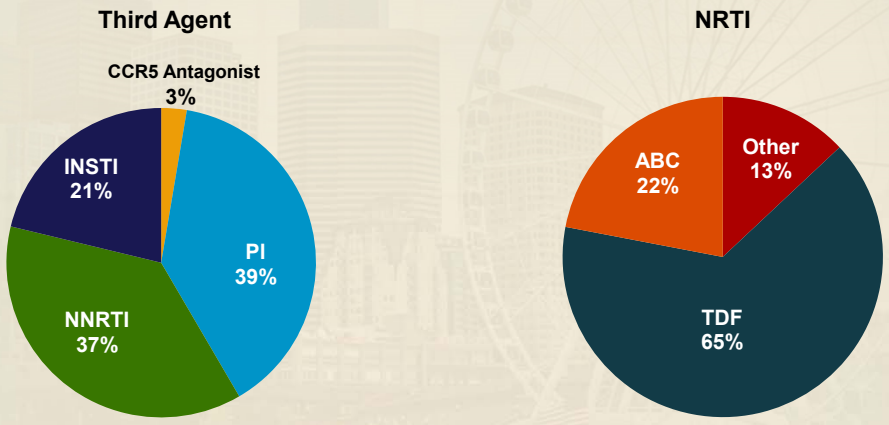
Antiretroviral Treatment Prior to Switching to E/C/F/TAF



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

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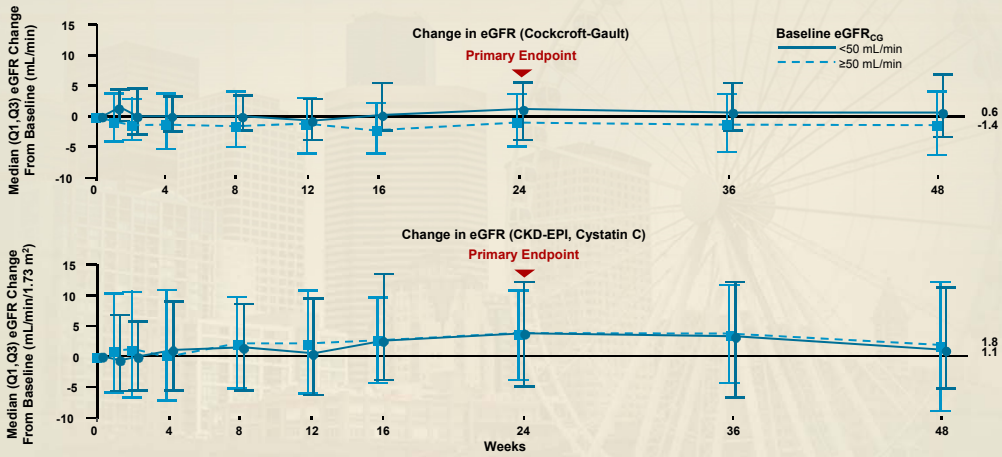
Change in eGFR from Baseline to Week 48



- 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 m^2
- There was no significant change in eGFR$_{CG}$ or eGFR$_{CKD\text{-}EPI,\ cystatin\ C}$ to Week 48

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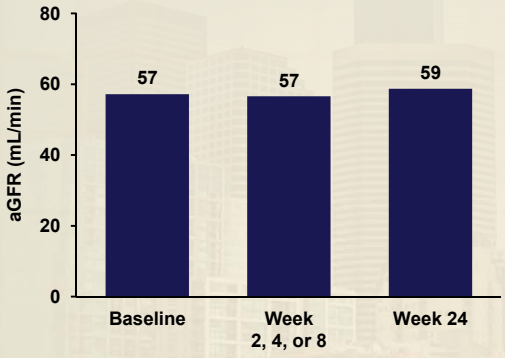
Actual GFR by Iohexol Clearance (n=32)



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

- 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)

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

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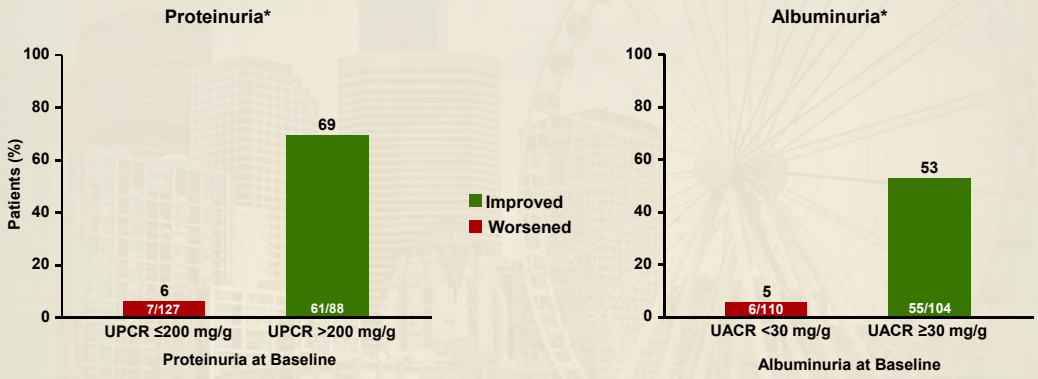
Proteinuria and Albuminuria: Improvement vs Worsening at Week 48



- **Decreased prevalence of clinically significant proteinuria and albuminuria**

*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.

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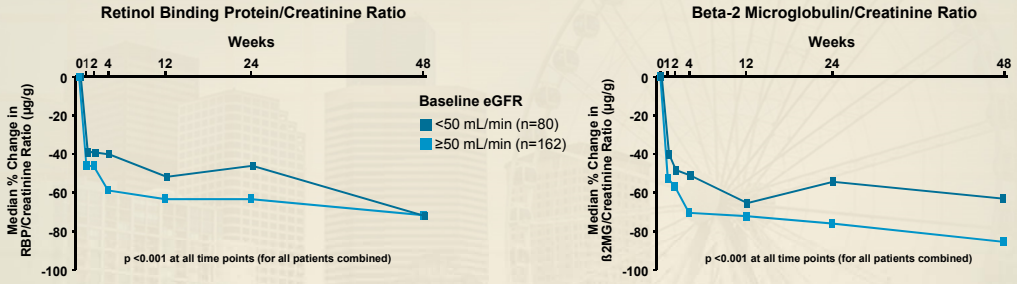
Measures of Renal Tubular Function



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 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)**

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

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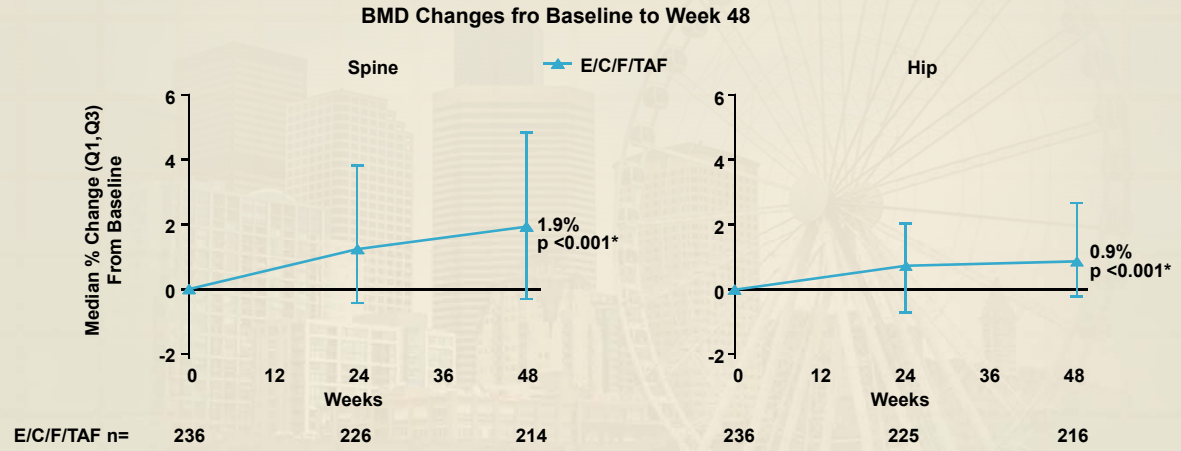
Change in Spine and Hip Bone Mineral Density



- 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

*Two-sided Wilcoxon signed-rank test.

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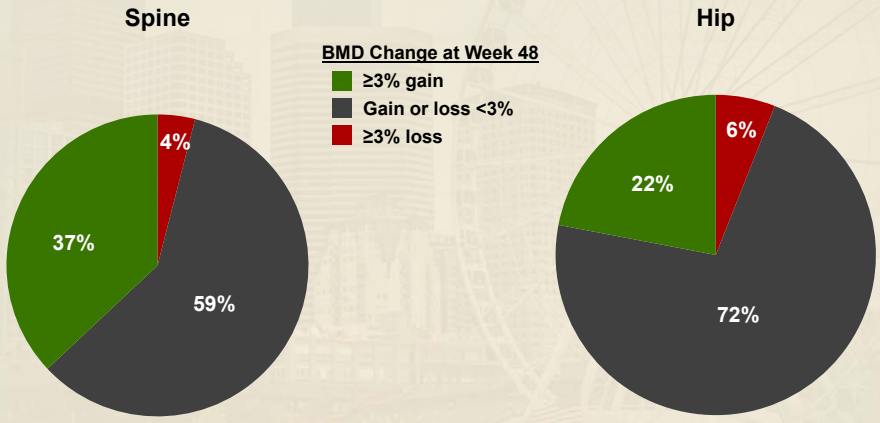
Proportions of Patients with Bone Mineral Density Changes



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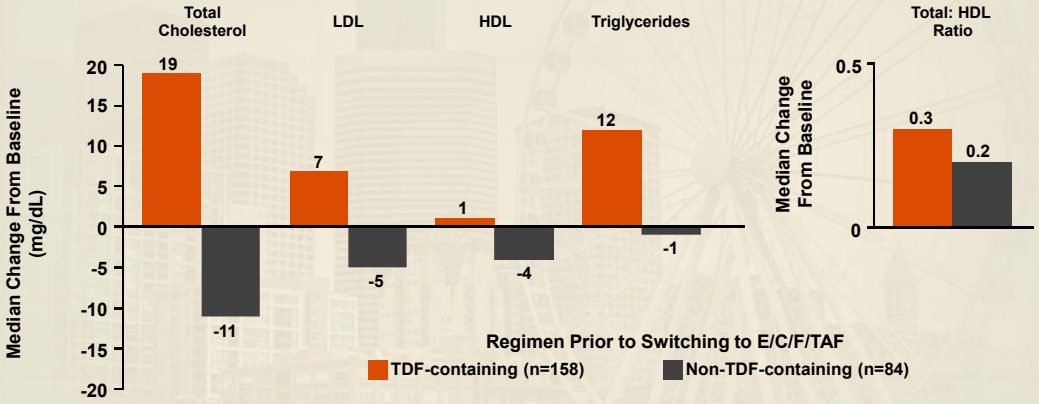
Switch to E/C/F/TAF in Mild-Moderate Renal Disease: Metabolic Changes at Week 48



- **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**

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Virologic Outcomes at Week 48 (FDA Snapshot) (1/2)

- **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 AEs by Week 48: renal failure, 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
  - 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

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Safety Summary

- **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**

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