Comparative Study of Tenofovir Alafenamide vs Tenofovir Disoproxil Fumarate, Each with Elvitegravir, Cobicistat, and Emtricitabine, for HIV Treatment

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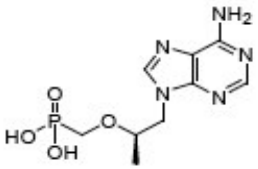
Summary

GS-US-292-0102 – Week 24 Analysis

- Treatment-naïve patients given either E/C/F/TAF or STB had high levels of virologic suppression through 24 weeks
  - No resistance to E/C/F/TAF occurred
- Patients who received E/C/F/TAF had a significantly smaller increase in serum creatinine
  - Changes in creatinine occurred in first 4 weeks
  - No renal discontinuations and no tubulopathy seen in either arm
  - Mechanism underlying difference in lower creatinine change is under investigation
- Patients who received E/C/F/TAF had a significantly smaller decrease in bone mineral density of hip and spine
- Two confirmatory Phase 3 studies are currently underway
  - Proactive efforts to increase participation of women
- Related Abstracts: #529 TAF PK in renal impairment; #540 TAF not OAT substrate

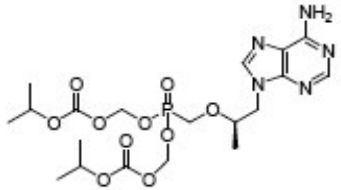
Tenofovir Alafenamide (TAF)

Next Generation Prodrug of Tenofovir



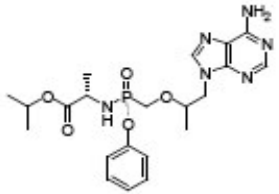
TFV

Tenofovir



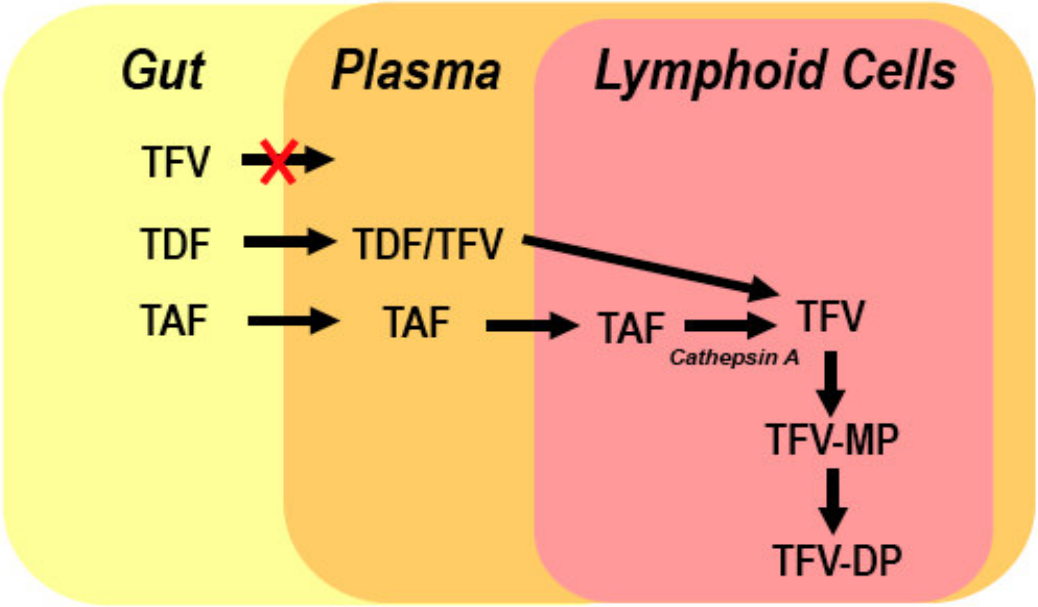
TDF

Tenofovir Disoproxil Fumarate



TAF

Tenofovir Alafenamide



Tenofovir Alafenamide (TAF)

Background (formerly GS-7340)

- **TAF is a prodrug of tenofovir (TFV) with increased delivery to lymphoid cells and hepatocytes**

- **Relative to TDF 300 mg, TAF 25 mg has[1]:**
  - Increased anti-HIV-1 activity in Phase 1
  - Increased intracellular TFV-DP levels by ~7-fold
  - Decreased circulating plasma TFV levels by ~90%
  - Lower levels of TFV in kidney and bone tissue expected

- **TAF formulated into a single tablet regimen as E/C/F/TAF**
  - Elvitegravir 150mg
  - Cobicistat 150mg
  - FTC (emtricitabine) 200mg
  - TAF 10mg

- **TAF 10mg in E/C/F/TAF has PK comparable to TAF 25mg alone[2]**
  - COBI ↑ TAF levels ~2.2-fold

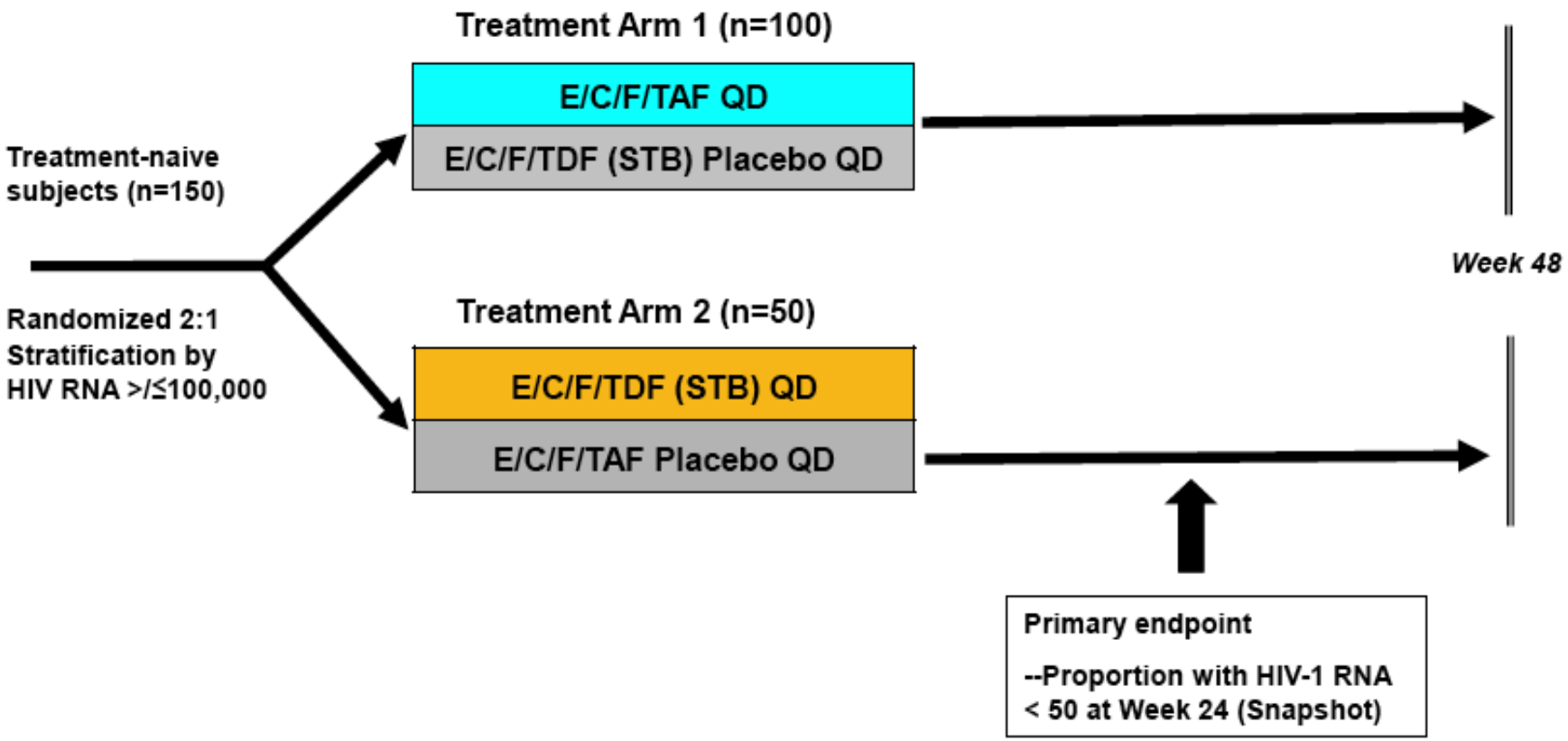
[1]P Ruane, et al. CROI 2012; Paper # 103

[2]S Ramanathan, et al. IWCPHT 2012; Abstract O_13

Phase 2 Study Design

GS-US-292-0102

Randomized, placebo-controlled, double-blind study



Baseline Characteristics

GS-US-292-0102 – Week 24 Analysis

Characteristic	E/C/F/TAF (n=112)	STB (n=58)
Age (years), Median	34	38
Male	96%	98%
White Race	67%	69%
Black Race (or African Descent)	30%	28%
Other Race	3%	3%
Hispanic or Latino Ethnicity	22%	19%
Asymptomatic HIV Infection	88%	91%
HBsAg, HCVAb Seropositive	0, 0	0, 0
HIV-1 RNA (log_{10}c/mL), Median	4.55	4.58
> 100,000 c/mL	17%	28%
CD4 count (cells/mm^3), Median	385	397
≤ 200	13%	19%
Estimated GFR (mL/min), Median – Cockcroft-Gault	115.2	113.3

Subject Disposition

GS-US-292-0102 – Week 24 Analysis

Week 24 data, n (%)	E/C/F/TAF (n=112)	STB (n=58)
Suppressed to < 50 copies/mL	97 (86.6%)	52 (89.7%)
Not suppressed	15 (13.4%)	6 (10.3%)
-- Never suppressed to <50	2 (1.8%)	3 (5.2%)
-- Suppressed with blip or rebound at W24	5 (4.5%)	3 (5.2%)
-- Discontinued due to adverse event*	4 (3.6%)	0
-- Data unavailable**	4 (3.6%)	0

FDA Snapshot

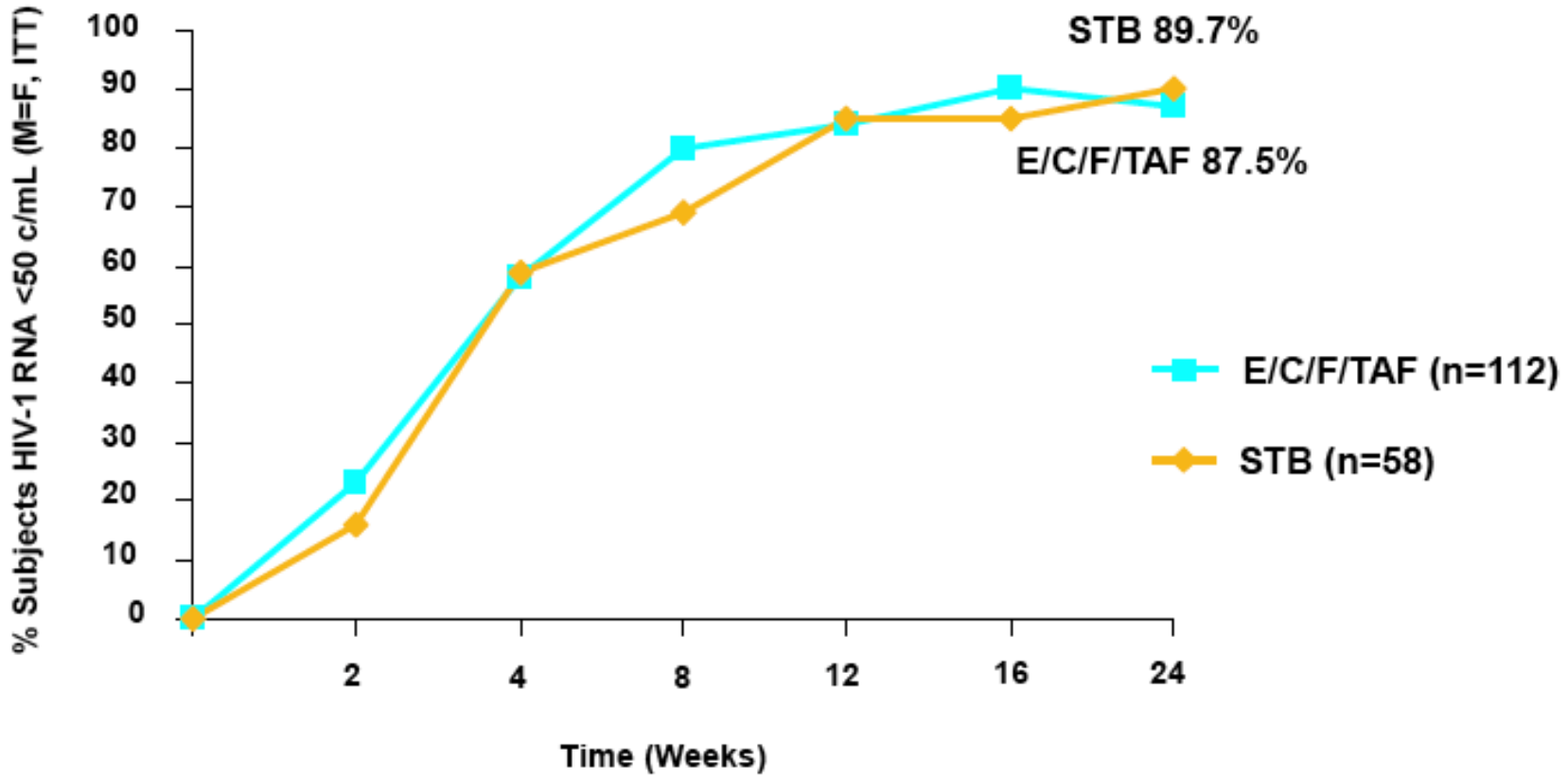
Weighted difference: -4.9% (95%CI, -15.7 to 5.9), p=0.36

*Coxsackie (1), MAC/CMV (1), Acute promyelocytic leukemia (1), flushing/photosensitivity (1)

**Lost to Follow-up (1), Administrative (1), Viral load collected outside window (2)

Virologic Response (M=F, ITT)

GS-US-292-0102 – Week 24 Analysis



- *Mean change from baseline CD4+ cell count:*
  - *E/C/F/TAF, +163 cells/μL*
  - *STB, +177 cells/μL (p = 0.76)*

Interim Resistance Analysis

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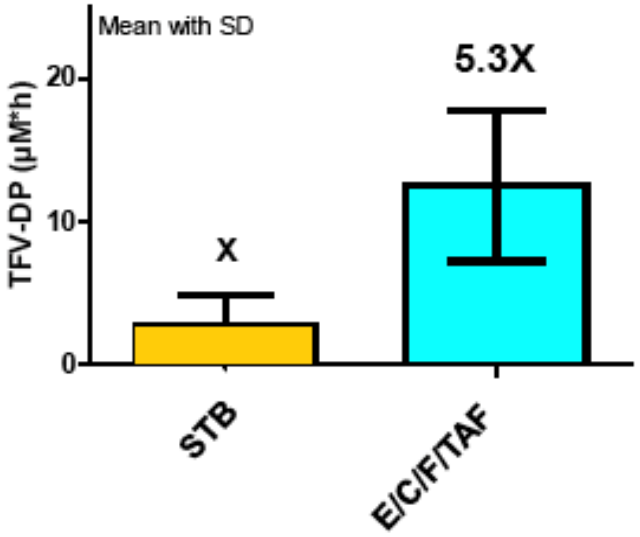
- 3 subjects met protocol-specified criteria for resistance analysis
  - Confirmed >400 copies/mL of HIV-1 RNA at Week 24 or the discontinuation visit
  - E/C/F/TAF arm (n=1)
    - 1 subject with Week 24 rebound
      - No resistance detected
  - STB arm (n=2)
    - 1 subject with persistent viremia
      - NRTI resistance (M184V + K70E)
      - No EVG resistance
    - 1 subject with late rebound
      - No resistance detected

TFV Plasma and TFV-DP Intracellular Levels

GS-US-292-0102 – Week 24 Analysis

PBMC TFV-DP $AUC_{0\text{-}24h}$ at Week 4 or 8



E/C/F/TAF

- *PBMC TFV-DP exposure was 5.3-fold higher (90% CI: 2.9 to 9.6)*
- *Plasma TFV exposure (AUC_{tau}) was 91% lower*

Plasma TFV PK Mean (%CV)	E/C/F/TAF (n=19)	STB (n=7)
C_{trough} (ng/ml)	11.4 (17.9)	82.8 (26.6)
AUC_{tau} (ng*hr/ml)	326.2 (14.8)	3795.2 (21.9)

Adverse Events

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Adverse Events occurring in at least 5% of subjects in E/C/F/TAF	E/C/F/TAF (n=112)	STB (n=58)
Any AE	91 (81%)	47 (81%)
Nausea	20 (18%)	7 (12%)
Diarrhea	13 (12%)	7 (12%)
Fatigue	13 (12%)	5 (9%)
Headache	11 (10%)	6 (10%)
Upper Respiratory Tract Infection	8 (7%)	7 (12%)
Flatulence	6 (5%)	2 (3%)

- *More than 90% of AEs in both arms were Grade 1 or 2*
- *There were no treatment-related SAEs in either arm*

Grade 3 or 4 Lab Abnormalities

GS-US-292-0102 – Week 24 Analysis

Maximum Toxicity Grade Post-Baseline, n (%)	E/C/F/TAF (n=112)	STB (n=58)
Any G3 or G4 abnormality	19 (17%)	8 (14%)
LDL	7 (6%)	2 (3%)
Neutropenia	5 (5%)	1 (2%)
White Blood Cells	1 (1%)	0
Amylase	2 (2%)	1 (2%)
Creatine Phosphokinase	6 (5%)	2 (3%)
Glucose	0	1 (2%)
Total cholesterol	1 (1%)	0
Triglycerides	1 (1%)	1 (2%)

- *There were more subjects with neutropenia in the E/C/F/TAF arm at baseline*

Fasting Metabolic Assessments

GS-US-292-0102– Week 24 Analysis

Assessment (median increase)	E/C/F/TAF (n=112)	STB (n=58)	*p-value*
Total Cholesterol (mg/dL)	31	15	<0.001
LDL (mg/dL)	17	4	0.001
HDL (mg/dL)	6	2	0.007
TC:HDL ratio	0.1	0.1	0.47
Triglycerides (mg/dL)	24	21	0.48
Fasting serum glucose (mg/dL)	3	3	0.78

Median Change in Serum Creatinine

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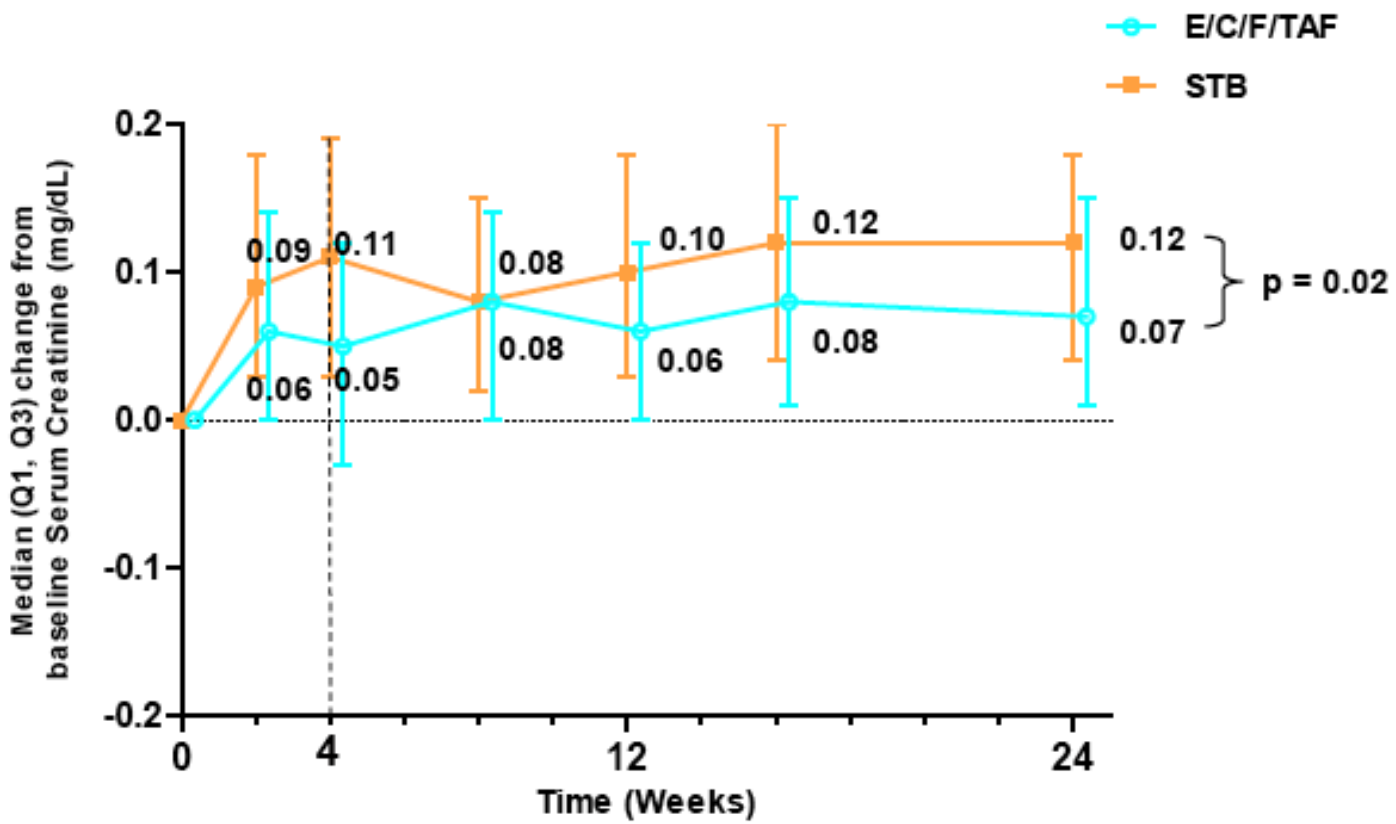
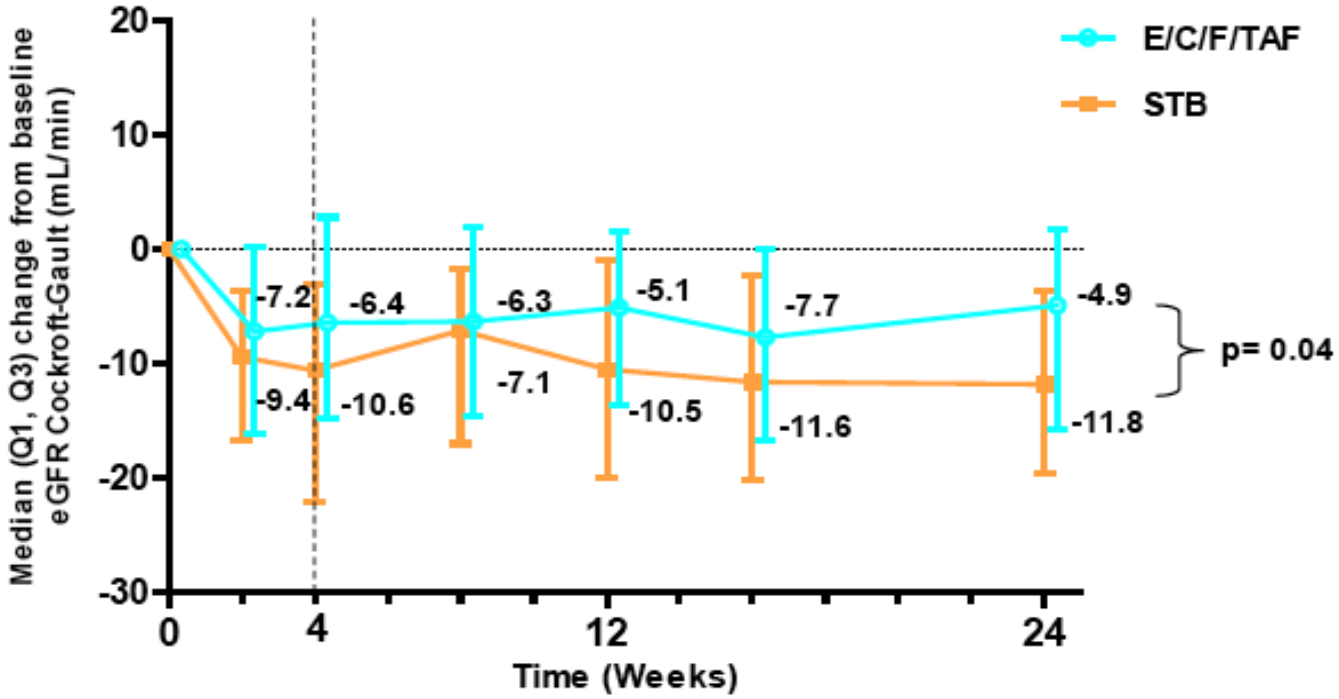


- *Change in serum creatinine at Week 24*
  - *E/C/F/TAF: 0.07 mg/dL*
  - *STB: 0.12 mg/dL (p=0.02)*

Median Estimated GFR (Cockcroft-Gault)

GS-US-292-0102 – Week 24 Analysis



- *Change in eGFR at Week 24*
  - *E/C/F/TAF: -4.8 mL/min*
  - *STB: -11.8 mL/min (p=0.04)*

Potential Markers of Renal Tubulopathy

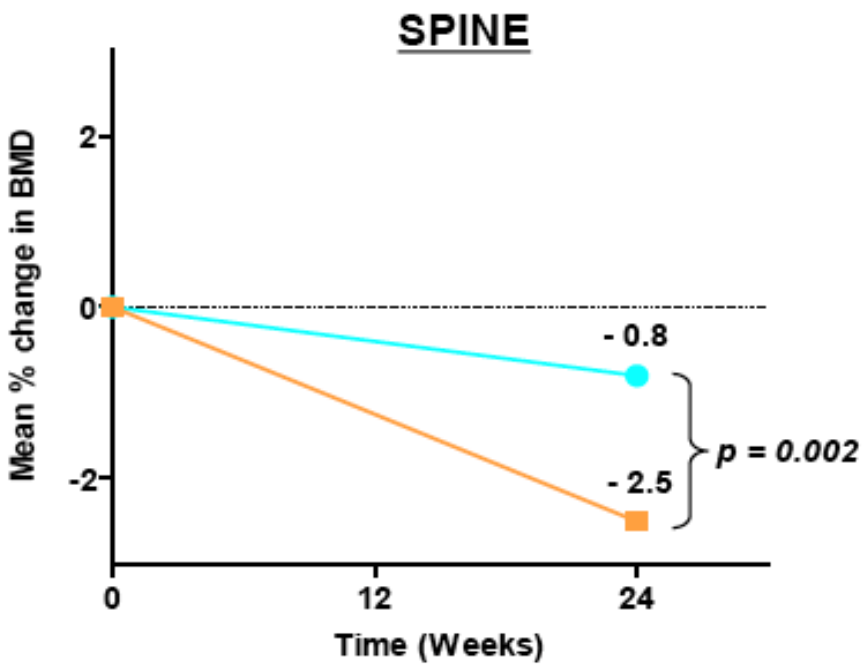
GS-US-292-0102 – Week 24 Analysis

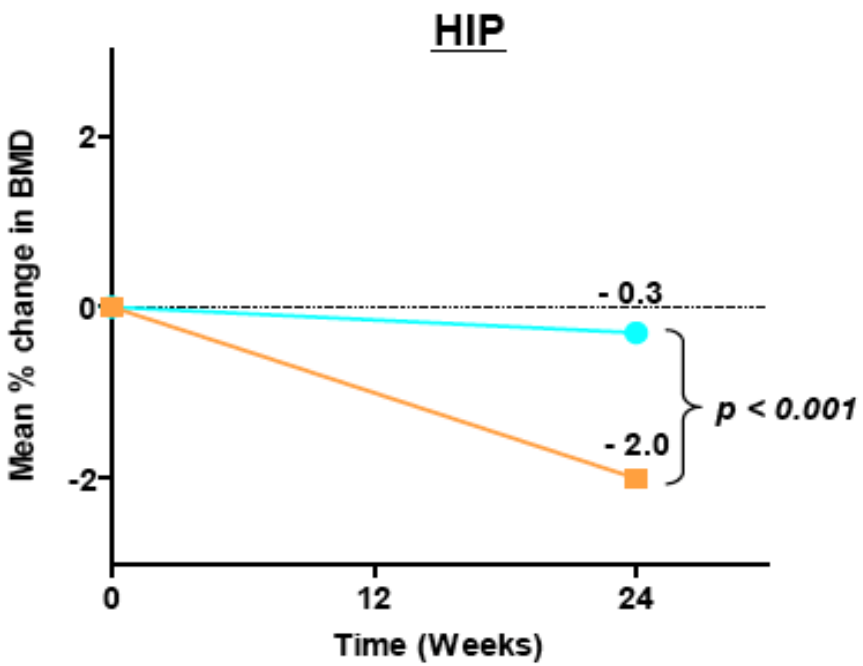
Test	E/C/F/TAF (n=112)	STB (n=58)
Serum phosphate (mg/dL)		
Normal	109 (98%)	54 (93%)
2.0 – 2.2	1 (0.9%)	3 (5.2%)
1.5 – 2.0	1 (0.9%)	1 (1.7%)
<1.5	0	0
Fractional excretion of PO_4 *change from baseline*	1.5	2.6
Glycosuria (dipstick)		
0	110 (99%)	58 (100%)
1+	1 (0.9%)	0
2+ or higher	0	0
Proteinuria (dipstick)		
0	97 (87%)	46 (79%)
1+	12 (10.8%)	11 (19.0%)
2+ or higher	3 (2.7%)	1 (1.7%)

- ***No renal AEs or discontinuations occurred***
- ***No cases of proximal renal tubulopathy seen***

Percent Change in Bone Mineral Density (DEXA)

GS-US-292-0102 – Week 24 Analysis





- *Proportion of subjects with no decrease in BMD*
  - *Spine: E/C/F/TAF, 38%; STB, 12%*
  - *Hip: E/C/F/TAF, 41%; STB: 23%*