SAT368

Evaluation of Renal and Bone Safety at 4 Years in Post-Liver Transplant Patients With Chronic Kidney Disease Receiving Tenofovir Alafenamide for HBV Prophylaxis

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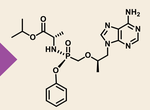
Introduction

- Infection with hepatitis B virus (HBV) remains an important indication for orthotopic liver transplantation (OLT), which can be associated with numerous complications postoperatively, including nephrotoxicity from use of calcineurin inhibitors, and osteoporosis secondary to preoperative malnutrition and postoperative corticosteroids[1]
  - Tenofovir disoproxil fumarate (TDF) given alone or with other antivirals is frequently used to prevent viral relapse post-OLT[2]
  - Results with other antivirals, including tenofovir alafenamide (TAF), are limited

TAF
Nucleotide reverse transcriptase inhibitor



Tenofovir Alafenamide

- Novel tenofovir prodrug; greater plasma stability, with enhanced hepatic delivery of active drug and lower circulating levels of tenofovir relative to TDF[3-6]
- Switching to TAF vs continued TDF showed noninferior efficacy at Weeks 48 and 96 in suppressed chronic HBV patients with/without compensated cirrhosis, including those with mild renal insufficiency and creatinine clearance (estimated glomerular filtration rate by Cockcroft-Gault method [$eGFR_{CG}$]) ≥50 mL/min when switched to TAF, with improved bone and renal safety[7-9]
- Week 192 results from the present study demonstrated that in patients with chronic HBV who were status post-OLT and had chronic kidney disease (CKD), switching to TAF maintained suppression of HBV, while bone and renal safety were improved compared with patients who continued to receive TDF[10]

Objective

- To evaluate the long-term renal and bone safety of TAF vs TDF when given as antiviral prophylaxis following OLT in patients with a pretransplant diagnosis of HBV and CKD through 192 wk

Methods

Study Design

OLE, open-label extension.

- Open-label, phase 2 study (GS-US-320-3912 [ClinicalTrials.gov NCT02862548])
  - Randomized phase: TAF 25 mg qd or continued TDF-containing treatment for 48 wk
  - OLE phase: all patients received TAF 25 mg qd through Week 192 (ie, TAF→TAF vs TDF→TAF)
- Key inclusion criteria:
  - Chronic HBV including patients with compensated cirrhosis maintained on TDF-containing regimen
  - OLT ≥12 wk prior to screening
  - HBV DNA < lower limit of quantitation; alanine aminotransferase (ALT) ≤10x upper limit of normal at screening
  - eGFR by Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$) <90 mL/min/1.73 m²
- 1:1 randomization: stratified by renal function ($eGFR_{CKD-EPI}$ < or ≥50 mL/min/1.73 m²) at screening

Exploratory Study Endpoints at Week 192

- **Overall safety:** adverse events (AEs) and laboratory abnormalities
- **Renal parameters:** changes in serum creatinine (sCr): eGFR by creatinine- and noncreatinine-based equations including chromium-51-labeled ethylenediaminetetraacetic acid (Cr-EDTA; mL/min/1.73 m²), CKD-EPI creatinine (mL/min/1.73 m²), CKD-EPI cystatin C (mL/min/1.73 m²), and CG (mL/min) methods; quantitative markers of tubular proteinuria
- **Bone parameters:** changes in bone mineral density (BMD) at spine and hip by dual-energy x-ray absorptiometry; serum markers of bone turnover

Results

Demographics and Disease Characteristics

	TAF n=26	TDF n=25
Mean age, y (range)	58 (26–76)	62 (45–77)
Men, n (%)	16 (62)	22 (88)
Asian, n (%)	7 (27)	10 (40)
Pacific Islander, n (%)	15 (58)	12 (48)
Mean BMI, kg/m² (range)	27.7 (20.5–35.8)	28.3 (16.7–39.3)
HBV DNA <20 IU/mL, n (%)	26 (100)	25 (100)
Mean ALT, U/L (SD)	28 (12.6)	38 (43.7)
Median sCr, mg/dL (Q1, Q3)	1.38 (1.23, 1.56)	1.33 (1.22, 1.55)
Median $eGFR_{Cr\text{-}EDTA\ renal\ scan}$, mL/min/1.73 m² (Q1, Q3)	56.2 (47.4, 65.7)	58.1 (43.7, 73.7)
Median $eGFR_{CKD\text{-}EPI}$, mL/min/1.73 m² (Q1, Q3)	48.8 (44.8, 59.2)	52.2 (45, 60.3)
<50 mL/min/1.73 m², n (%)	15 (58)	12 (48)
Median $eGFR_{CKD\text{-}EPI\ cystatin\ C}$, mL/min/1.73 m² (Q1, Q3)	63.9 (47.0, 79.3)	68.2 (53.7, 80.3)
Median $eGFR_{CG}$, mL/min (Q1, Q3)	57.3 (44.7, 73.5)	65.5 (46.2, 74.0)
Current calcineurin inhibitor use, n (%)	21 (81)	19 (76)
Prior TDF exposure, n (%)	26 (100)	25 (100)
Median total TDF exposure prior to study Day 1, wk (Q1, Q3)	294 (244, 317)	294 (178, 337)
Median y since transplant (Q1, Q3)	9 (3, 14)	9 (4, 12)
History of rejection, n (%)	0	2 (8)
Multiple organ transplant, n (%)	1 (4)*	0
HBeAg positive, n (%)	1 (4)	0
HBsAg positive, n (%)	2 (8)	1 (4)

*Renal transplant. BMI, body mass index; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; Q, quartile; SD, standard deviation.

- 23 patients in each group completed the study at Week 192
- All patients with nonmissing data had sustained viral suppression at Week 192

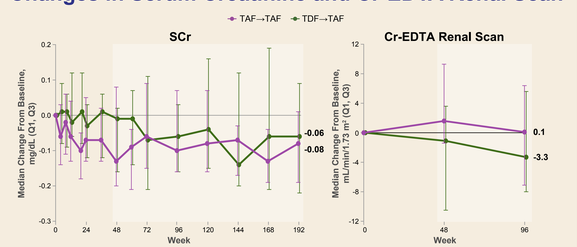
Safety Summary

	Randomized Phase		OLE	
n (%)	TAF n=26	TDF n=25	TAF→TAF n=26	TDF→TAF n=24
Any AE	**24 (92)**	**24 (96)**	**25 (96)**	**24 (100)**
Grade 3–4 AE	2 (8)	6 (24)	6 (23)	8 (33)
Related to study drug	0	0	0	0
Serious AE	3 (12)	7 (28)	8 (31)	8 (33)
Related to study drug	0	0	0	0
Discontinued study drug due to AE	0	1 (4)*	1 (4)†	0
Death	0	1 (4)‡	2 (8)§	0
Renal or bone AEs in ≥2 patients				
Bone density decreased	3 (12)	1 (4)	1 (4)	1 (4)
Acute kidney injury	0	0	2 (8)	5 (21)
Nephrolithiasis	0	0	0	3 (13)
Nocturia	0	0	0	2 (8)

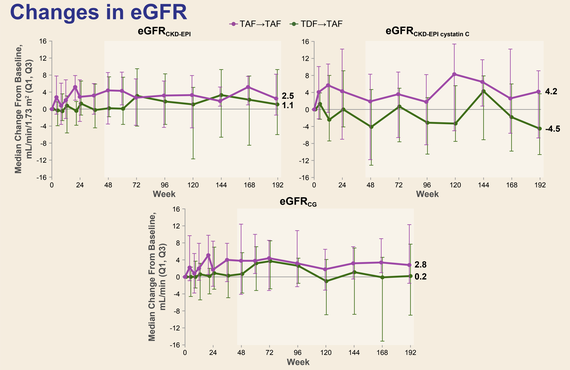
*Disseminated tuberculosis; †Acute kidney injury (AKI) not related to study drug; ‡Diagnosed with diffuse large B-cell lymphoma during treatment; §Liver failure and cardiac arrest.

- AKI occurred in 7 patients during OLE
- No AKI was considered study drug related
- All patients with AKI had preexisting or predisposing factors, which most likely triggered the acute decline in renal function
  - All had CKD stage ≥2 pretreated with nephrotoxic medications, eg, tacrolimus
  - Renal comorbidities (hypertension and/or diabetes) that were managed with nephrotoxic agents (n=6)
  - Age ≥65 y (n=3)
  - Concurrent renal triggers at the time of AKI onset, eg, AEs of anemia, diarrhea, urosepsis, and fluid overload (n=6)
- Only 1 patient with AKI had study drug discontinued

Changes in Serum Creatinine and Cr-EDTA Renal Scan



Changes in eGFR



- In the randomized phase, patients on TAF had improved eGFR values, which remained stable through Week 192
- In patients on TDF→TAF, eGFR remained stable through Week 192

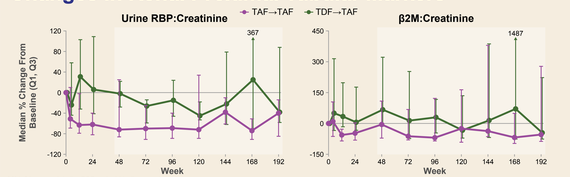
Shifts in CKD Stages

		Baseline							
		TAF→TAF: n=26				TDF→TAF (n=25)			
CKD Stage n (%)		1 n=0	2 n=5	3a n=14	3b n=7	1 n=0	2 n=7	3a n=11	3b n=7
Week 48	1	0	1 (20)	0	0	0	0	0	0
	2	0	3 (60)	5 (36)	0	0	5 (71)	2 (22)	1 (17)
	3a	0	1 (20)	5 (36)	4 (57)	0	2 (29)	6 (67)	1 (17)
	3b	0	0	4 (29)	3 (43)	0	0	1 (11)	4 (67)
	1	0	0	0	0	0	0	0	0
	2	0	2 (67)	4 (33)	1 (20)	0	4 (67)	3 (33)	1 (20)
	3a	0	1 (33)	7 (58)	0	0	1 (17)	4 (44)	1 (20)
	3b	0	0	1 (8)	4 (80)	0	1 (17)	1 (11)	2 (40)
Week 192	4	0	0	0	0	0	0	1 (11)	0
	5	0	0	0	0	0	0	0	1 (20)

Worsened Stable Improved

- Consistent with entry criteria, all patients were categorized as having CKD stage 2 or 3 (based on $eGFR_{CKD-EPI}$) at baseline
- Most patients remained stable or had improvement in CKD stage through 4 y

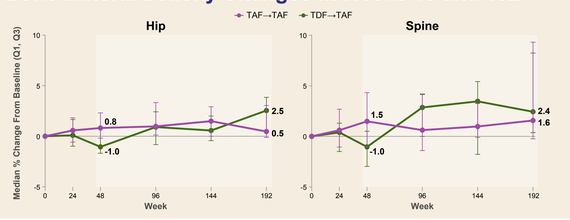
Changes in Renal Proximal Tubular Markers



β2M, β2-macroglobulin; RBP, retinol-binding protein.

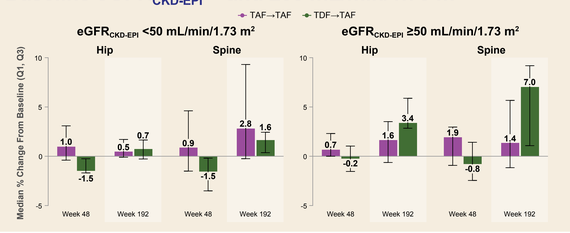
- At Week 192, changes in both markers were similar for the TAF→TAF and TDF→TAF groups

Bone Mineral Density Changes at Weeks 48 and 192



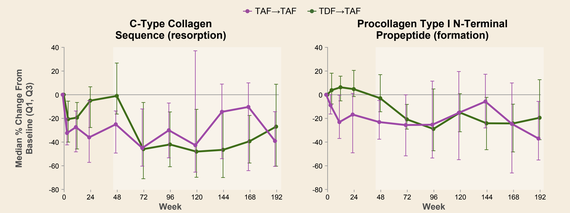
- TAF treatment resulted in greater improvements in hip and spine BMD vs continued treatment with TDF-containing regimens in the randomized phase
- In the TDF→TAF group, BMD improvements were observed after switching to TAF through Week 192

Bone Mineral Density Changes at Weeks 48 and 192 by Baseline $eGFR_{CKD-EPI}$ < and ≥50 mL/min/1.73 m²



- In the randomized phase, patients on TDF with baseline $eGFR_{CKD-EPI}$ <50 mL/min/1.73 m² had greater declines in BMD vs patients with baseline $eGFR_{CKD-EPI}$ ≥50 mL/min/1.73 m²
- In contrast during the randomized phase, similar increases were seen in patients on TAF regardless of baseline $eGFR_{CKD-EPI}$
- At Week 192, patients who remained on TAF showed BMD improvement regardless of baseline renal function and patients on TDF→TAF had improved BMD in the OLE

Bone Biomarkers Over 192 Weeks



- At Week 192, changes in both markers were similar for the TAF→TAF and TDF→TAF groups

Conclusions

- Long-term results in OLT recipients with CKD switching from TDF-containing regimens to TAF monotherapy demonstrated that prevention of viral relapse was maintained
- Switching from TDF to TAF was safe and well tolerated; overall during OLE, safety results were similar across both treatment groups
  - Continued improved renal safety profile compared with TDF was observed in this high-risk patient population after switching to TAF
  - Renal AEs reflect the underlying post-OLT population; all patients with AKI had predisposing factors, including multiple renal comorbidities and nephrotoxic medications, and most had concurrent AEs, including infectious causes, which likely triggered the acute decline in renal function
  - Continued improved bone safety profile compared with TDF was observed regardless of baseline renal function

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