Safety and Efficacy at 48 Weeks After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Chronic HBV Patients With Risk Factors for TDF Use

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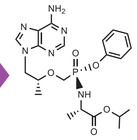
Introduction

- Tenofovir alafenamide (TAF), a novel tenofovir prodrug, has shown noninferior efficacy to tenofovir disoproxil fumarate (TDF), with a superior bone and renal safety profile through 96 weeks in viremic chronic hepatitis B (CHB) patients, and 48 weeks in virally suppressed patients switched from TDF to TAF[1,2]
- TAF is a preferred treatment in the current European Association for the Study of the Liver (EASL) and AASLD hepatitis B virus (HBV) guidelines,[3,4] particularly for patients with risk factors for TDF-associated renal and bone effects

TAF
Nucleotide reverse transcriptase inhibitor



Objectives

- To assess safety and efficacy at Week 48 in virally suppressed CHB patients with TDF risk factors who were switched from TDF to TAF

Methods

Study Design
Study 4018

- Randomized, double-blind, active controlled, Phase 3 study (NCT02979613)
- Key inclusion criteria: hepatitis B e antigen (HBeAg)-negative and -positive patients with/without compensated cirrhosis, and having estimated glomerular filtration rate by Cockcroft-Gault equation ($eGFR_{CG}$) ≥50 mL/min
- Stratified by HBeAg status and age (< vs ≥50 y)

Population: Patients With ≥1 Baseline Risk Factor for TDF

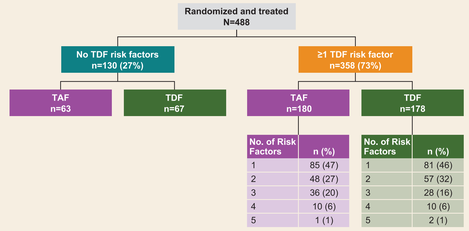
Baseline Condition	Analysis
Advanced age	>60 y*
Bone diseases	Osteoporosis by hip or spine T-score*
Renal impairment	CKD stage ≥2 (baseline $eGFR_{CG}$ <90 mL/min)†
Albuminuria	UACR >30 mg/g*
Hypophosphatemia	Serum phosphate <2.5 mg/dL*
Obesity	BMI ≥30 kg/m²
Comorbidities	CVD, DM, HL, or HTN

*Risk factor for TDF use in EASL HBV guidelines 2017; †eGFR <60 mL/min/1.73 m² used in EASL HBV guidelines.
BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension; UACR, urine albumin:creatinine ratio.

- Safety assessments:
  - Renal: serum creatinine, $eGFR_{CG}$, and urine biomarkers of tubular function
  - Bone: serial dual energy X-ray absorptiometry scans at hip/spine and serum bone biomarkers
- Efficacy assessments:
  - Viral suppression: HBV DNA <20 IU/mL
  - Normal alanine aminotransferase (ALT) by 2018 AASLD criteria (≤25 and ≤35 U/L for females and males, respectively) and by central laboratory criteria (≤34 and ≤43 U/L for females and males, respectively, aged <69 y; ≤32 and ≤35 U/L aged >69 y)

Results

Patient Disposition



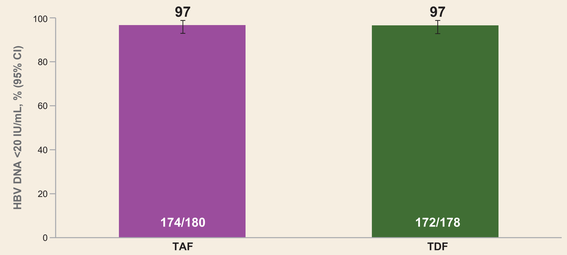
- At baseline, the majority of patients (73%) had ≥1 risk factor, while ~25% had ≥3 risk factors

Baseline Demographics and Characteristics

	Parameter	No TDF Risk Factors		≥1 TDF Risk Factor	
		TAF n=63	TDF n=67	TAF n=180	TDF n=178
Demographics	Mean age, y (range)	44 (21–58)	44 (25–58)	53 (26–84)	54 (24–83)
	Female, n (%)	11 (17)	12 (18)	53 (29)	67 (38)
	Race/ethnicity, n (%)				
	Asian	52 (83)	60 (90)	143 (79)	145 (82)
	Black/African-American	3 (5)	3 (4)	6 (3)	5 (3)
	White	8 (13)	4 (6)	30 (17)	27 (15)
	Median BMI, kg/m² (range)	24 (19–29)	25 (18–29)	24 (17–46)	24 (16–38)
Disease Characteristics	HBeAg-positive, n (%)	26 (41)	26 (39)	52 (29)	53 (30)
	HBV DNA <20 IU/mL, n (%)	61 (97)	66 (99)	177 (98)	176 (99)
	Median ALT, U/L (Q1, Q3)	27 (19, 35)	25 (19, 30)	23 (18, 31)	23 (17, 31)
	FibroTest™* score ≥0.75, n (%)	2 (3)	2 (3)	22 (12)	15 (8)
Renal Function	Median $eGFR_{CG}$, mL/min (Q1, Q3)	107 (98, 118)	105 (95, 116)	85 (73, 99)	84 (71, 98)
Baseline TDF Risk Factors (per EASL guidelines)	Advanced age (>60 y), n (%)	N/A	N/A	43 (24)	52 (29)
	Bone disease, n (%)	N/A	N/A	34 (19)	29 (16)
	Renal impairment, n (%)	N/A	N/A	117 (65)	121 (68)
	Albuminuria, n (%)	N/A	N/A	28 (16)	25 (6)
	Hypophosphatemia, n (%)	N/A	N/A	14 (8)	16 (4)
	Obesity, n (%)	N/A	N/A	19 (11)	15 (8)
	Comorbidities, n (%)	N/A	N/A	79 (44)	71 (40)

*BioPredictive S.A.S, Paris, France. N/A, not applicable; Q, quartile.

HBV DNA <20 IU/mL at Week 48 in Patients With ≥1 TDF Risk Factor*



*Analysis is by missing = failure. CI, confidence interval.

- Viral suppression was well maintained in CHB patients with TDF risk factors who switched from TDF to TAF
- Viral suppression was also maintained in CHB patients without TDF risk factors who switched from TDF to TAF (TAF 95% and TDF 96%)

Normal ALT at Week 48

Parameter	No TDF Risk Factors		≥1 TDF Risk Factor	
	TAF n=63	TDF n=67	TAF n=180	TDF n=178
2018 AASLD criteria	49 (78)	49 (73)	143 (79)	135 (76)
Central laboratory	55 (87)	56 (84)	162 (90)	152 (85)

- Rates of normal ALT levels in patients with risk factors were numerically higher with TAF vs TDF and comparable to the overall study population results
- In CHB patients with TDF risk factors, low rates of HBeAg seroconversion (TAF 4% and TDF 0%) were seen at Week 48; no patients with risk factors in either group had hepatitis B surface antigen seroconversion at Week 48

Safety

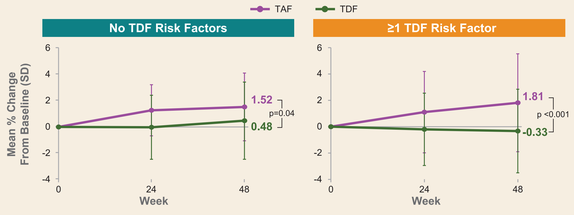
Parameter, n (%)	No TDF Risk Factors		≥1 TDF Risk Factor	
	TAF n=63	TDF n=67	TAF n=180	TDF n=178
Any AE	33 (52)	37 (55)	93 (52)	81 (46)
Grade 3–4 AE*	2 (3)	0	6 (3)	4 (2)
Serious AE*	3 (5)	2 (3)	8 (4)	1 (1)
D/C due to AE†	1 (2)	0	1 (1)	0
Death	0	0	0	0

*No Grade 3-4 adverse events (AEs) or serious AEs were related to study drug or reported in >1 patient; †Discontinuations (D/C) due to AEs of breast cancer (risk factor group) and alopecia (no risk factor group; n=1 each).

Changes in Hip Bone Mineral Density

SD, standard deviation.

Changes in Spine Bone Mineral Density



References: 1. Agarwal K, et al. J Hepatol 2015;62:533-40; 2. Lampertico P, et al. EASL 2019, poster FRI-183; 3. EASL. J Hepatol 2017;67:370-98; 4. Terrault NA, et al. Hepatology 2018;67:1560-99.

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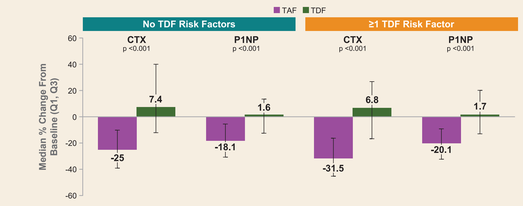
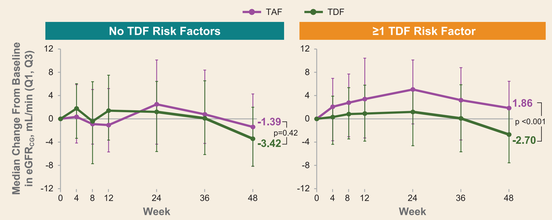
Bone Biomarkers at Week 48

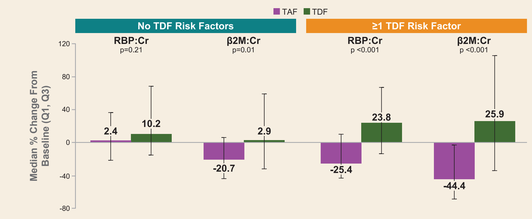


CTX, C-terminal telopeptide of type 1 collagen; P1NP, N-terminal propeptide of type 1 procollagen.

Change in $eGFR_{CG}$ Over 48 Weeks



Quantitative Markers of Tubular Proteinuria at Week 48



β2M:Cr, β2-microglobulin:creatinine ratio; RBP:Cr, retinol-binding protein:creatinine ratio.

- In CHB patients with TDF risk factors, switching to TAF resulted in improved creatinine clearance and renal tubular markers at Week 48 compared with continuing TDF
- As would be expected in patients with no risk factors and having normal renal function at baseline ($eGFR_{CG}$ >90 mL/min), changes in renal parameters were minimal on switching to TAF from TDF

Conclusions

- Switching from TDF to TAF for 48 weeks demonstrated significant improvements in both bone and renal parameters in CHB patients with ≥1 TDF risk factor at baseline for bone or renal toxicity
- In patients with no risk factors at baseline, switching to TAF for 48 weeks also demonstrated a significant improvement in bone parameters, with a trend towards improvement in renal parameters
- In all patients, high rates of antiviral efficacy were maintained with TAF and were similar to those in patients treated with TDF