Bone and Renal Safety of Tenofovir Alafenamide at 8 Years in Chronic HBV Patients With Underlying Risk Factors for Use of Tenofovir Disoproxil Fumarate

Maria Buti[1,2], Edward J Gane[3], Kosh Agarwal[4], Grace Wong[5], Young-Suk Lim[6], Chi-Yi Chen[7], Seng Gee Lim[8], Hiroshi Yatsuhashi[9], Scott K Fung[10], Frida Abramov[11], Hongyuan Wang[11], Leland J Yee[11], John F Flaherty[11], Calvin Q Pan[12], Patrick Marcellin[13]

[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [2]CIBEREHD del Instituto Carlos III, Madrid, Spain; [3]Auckland Clinical Studies, Auckland, New Zealand; [4]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom; [5]Medical Data Analytics Centre (MDAC), the Chinese University of Hong Kong, Hong Kong, China; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [7]Chiayi Christian Hospital, Chiayi, Taiwan; [8]National University Health System, Singapore; [9]Clincal Research Center, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; [10]University of Toronto, Department of Medicine, Toronto, Canada; [11]Gilead Sciences, Inc., Foster City, CA, USA; [12]NYU Langone Health, New York University Grossman School of Medicine, New York, NY, USA; [13]Hepatology Department, Hôpital Beaujon, APHP, INSERM, University of Paris, Clichy, France.

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Key Findings

- **In a subset of patients with CHB considered to be at risk for bone and/or renal toxicity from TDF, long-term TAF treatment over 8 years demonstrated the following:**
  - **Mean % declines in hip and spine BMD were small among patients treated with TAF, and decreases observed during TDF treatment were generally reversible following the switch from TDF to TAF**
  - **Small declines in $eGFR_{CG}$ were observed with TAF treatment. Among patients switched from TDF to TAF, greater recovery in $eGFR_{CG}$ was observed in those who switched from TDF to TAF after 2 years (TDF→TAF OL6y) vs after 3 years (TDF→TAF OL5y)**

Conclusions

Long-term treatment with TAF maintained a favorable renal and bone safety profile in patients with and without baseline risk factors for TDF-associated toxicities

These findings support guideline recommendations for the use of TAF as a preferred treatment option in patients with, or with the potential for, risk factors for TDF-associated toxicities

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Introduction

- Hepatitis B virus (HBV) infection is a major global health problem, and worldwide, approximately 316 million individuals are living with chronic HBV (CHB) infection[1]
- Nucleos(t)ide analogues, such as entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF), are recommended for the treatment of CHB[2-4]
- TAF, a novel tenofovir prodrug with enhanced plasma stability and more efficient hepatic delivery, has ~90% lower circulating levels of tenofovir relative to TDF when given at a lower daily dose than TDF[5,6]
- In 2 randomized, Phase 3 studies (Studies 108 and 110), TAF showed noninferior efficacy with improved renal and bone safety vs TDF at weeks 48 and 96[7-9]
- Several treatment guidelines recommend using TAF as an alternative first-line treatment to TDF for patients with underlying, or those with potential, risk factors for TDF-associated renal and bone toxicities[2,10]

TAF
Nucleotide reverse transcriptase inhibitor

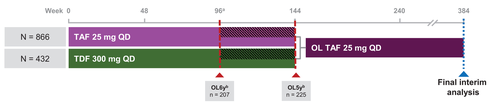
Objective

- To evaluate the long-term safety of TAF in patients with CHB enrolled in 2 Phase 3 studies, including in patients switched from TDF to TAF, who were considered to be at risk at baseline for adverse bone and/or renal effects from TDF based on the 2017 EASL guidelines

Methods

Study Design

Key inclusion criteria
- HBV DNA ≥20,000 IU/mL
- ALT >60 U/L (males) and >38 U/L (females) and ≤10 × ULN
- With/without compensated cirrhosis
- Treatment naïve or treatment experienced
- $eGFR_{CG}$ ≥50 mL/min

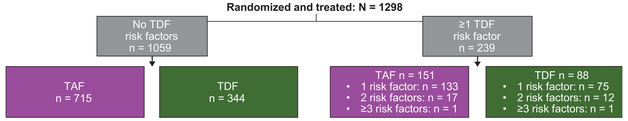


[a]Amendment 3 enacted to extend DB to week 144 and OL to week 384 (y8). Shaded/slashed areas represent patients who rolled over to OL TAF at week 96 (OL6y). [b]Patients who received DB TDF followed by OL TAF. ALT, alanine aminotransferase; DB, double-blind; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBV, hepatitis B virus; OL, open-label; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; y, year.

- Two Phase 3, randomized, double-blind studies in patients with CHB who were hepatitis B e antigen (HBeAg)-negative (Study 108, NCT01940341)[7,8] and HBeAg-positive (Study 110, NCT01940471)[7,9] were conducted
  - **Double-blind (DB) phase:** randomized 2:1 (TAF 25 mg:TDF 300 mg once daily) and stratified by HBV DNA level and treatment status (naïve/experienced)
  - **Open-label (OL) phase:** TAF 25 mg once daily in patients who received TAF or who received TDF for 2 (TDF→TAF OL6y) or 3 years (TDF→TAF OL5y)
- Risk factors (at baseline) for TDF-associated renal and bone toxicities
  - Age >60 years
  - Osteoporosis (T-score of less than −2.5 based on dual-energy X-ray absorptiometry (DXA) scan at hip and/or spine)
  - Estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) <60 mL/min
  - Ratio of urine albumin to creatinine >30 mg/g
  - Serum phosphorus <2.5 mg/dL
- Safety endpoints (pooled analysis of Study 108 and Study 110)
  - Key renal and bone safety parameters in patients with risk factors compared to those without risk factors
    - Bone parameters: serial DXA scans at hip and spine and serum bone biomarkers
    - Renal parameters: $eGFR_{CG}$ and urinary biomarkers of tubular function

Results

Distribution by TDF Risk Factor vs No Risk Factors



TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Of 1298 randomized and treated patients, 239 (18%) had at least 1 risk factor for TDF-associated renal and bone toxicity

Baseline Demographics and Characteristics

	Parameter	All Patients: TAF n = 866	All Patients: TDF→TAF n = 432	≥1 TDF Risk Factor: TAF n = 151	≥1 TDF Risk Factor: TDF→TAF n = 88
Demographics	Age, years, mean (range)	40 (18, 80)	41 (18, 72)	48 (20, 80)	49 (25, 72)
	Male	544 (63)	275 (64)	91 (60)	53 (60)
	Race				
	Asian	687 (79)	333 (77)	122 (81)	70 (80)
	White	167 (19)	87 (20)	26 (17)	18 (20)
	Black/African American	7 (1)	6 (1)	1 (1)	0
	Native Hawaiian/Pacific Islander	3 (<1)	3 (1)	2 (1)	0
	Other	2 (<1)	3 (1)	0	0
Disease characteristics	HBeAg negative	297 (36)	142 (33)	73 (48)	40 (46)
	FibroTest score ≥0.75, n/n (%)	76 (9)	42 (10)	26/145 (18)	14/87 (16)
	Diabetes	57 (7)	29 (7)	17 (11)	15 (17)
	Hypertension	99 (11)	62 (14)	35 (23)	29 (33)
	Cardiovascular disease	28 (3)	14 (3)	5 (3)	4 (5)
	Nucleos(t)ide experienced	211 (24)	108 (25)	37 (25)	20 (23)
Renal function	$eGFR_{CG}$, mL/min, median (Q1, Q3)	106 (91, 125)	105 (90, 124)	95 (91, 113)	98 (81, 118)
Baseline TDF risk factors	Age >60 years	42 (5)	28 (6)	42 (28)	28 (32)
	Osteoporosis of hip/spine	60 (7)	30 (7)	60 (40)	30 (34)
	$eGFR_{CG}$ <60 mL/min	5 (<1)	4 (<1)	5 (3)	4 (5)
	UACR >30 mg/g	44 (5)	28 (6)	44 (29)	28 (32)
	Serum phosphate <2.5 mg/dL	19 (2)	12 (3)	19 (13)	12 (14)

Data are reported as n (%) unless otherwise specified. $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UACR, ratio of urine albumin to creatinine.

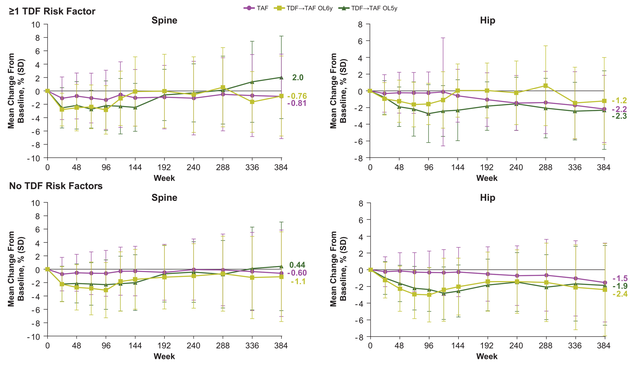
Open-Label Safety Summary

Patients, n (%)	All Patients n = 1157: TAF n = 775	All Patients n = 1157: TDF→TAF n = 382	≥1 TDF Risk Factor n = 211: TAF n = 131	≥1 TDF Risk Factor n = 211: TDF→TAF n = 80
Any AE	525 (68)	271 (71)	89 (68)	59 (74)
Grade 3 or 4 AE	60 (8)	27 (7)	12 (9)	13 (16)
Study drug-related Grade 3 or 4 AE	2 (<1)	0	0	0
Serious AE	97 (13)	49 (13)	25 (19)	16 (20)
Study drug-related serious AE	4 (<1)	0	0	0
D/C due to AE	9 (1)	3 (1)	1 (1)	1 (1)
Death[a]	1 (<1)	0	0	0

Open-label safety analysis set, open-label phase.
[a]Treatment emergent death; low-differential pancreatic adenocarcinoma.
AE, adverse event; D/C, discontinuation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Comparable overall safety was observed among patients with TDF risk factors and the overall population
- A numerically higher percentage of patients with ≥1 TDF risk factor had Grade 3 or 4 adverse events (AEs) or serious AEs, however, rates of study drug-related Grade 3 or 4 AEs or serious AEs were low and similar (<1%) across both populations

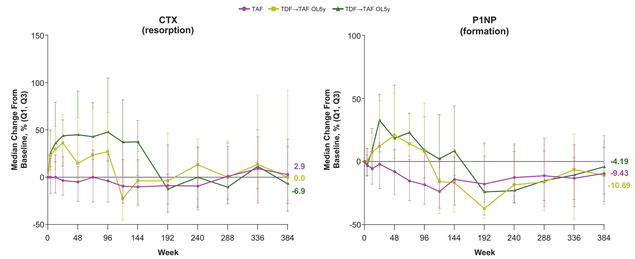
Changes in Hip and Spine BMD Over 8 Years



BMD, bone mineral density; OL, open-label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Among patients receiving continuous TAF treatment, mean % changes in hip and spine bone mineral density (BMD) were small regardless of risk factor status
- In the TDF→TAF groups, mean % increases in hip and spine BMD occurred after switching from TDF to TAF, indicating that TDF-induced bone loss can be reversible, including in patients with risk factors

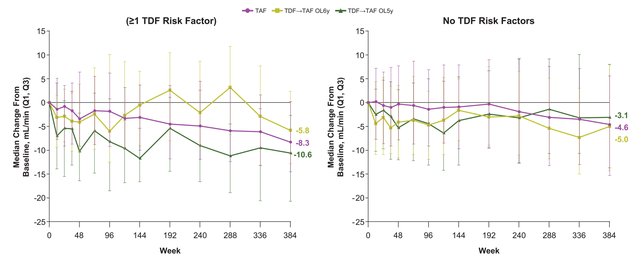
Changes in Serum Bone Biomarkers Over 8 Years Among Patients With ≥1 TDF Risk Factor



CTX, C-terminal telopeptide of type 1 collagen; OL, open-label; P1NP, N-terminal propeptide of type 1 procollagen; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; Y, year.

- Serum markers of bone turnover remained stable over 8 years among patients receiving TAF who had ≥1 TDF risk factor
- After switching from TDF to TAF, serum markers of bone turnover decreased and then stabilized among patients with ≥1 TDF risk factor (similar findings were seen in patients without risk factors; data not shown)

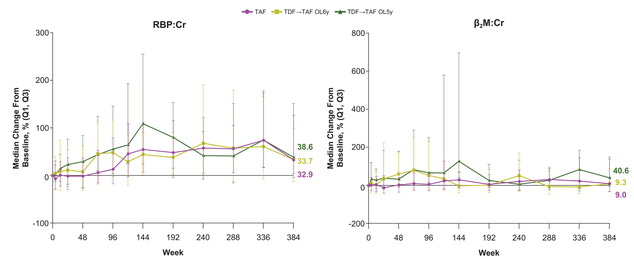
Changes in $eGFR_{CG}$ Over 8 Years



$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; OL, open-label; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

- Similar small median changes in $eGFR_{CG}$ were observed during the DB phase in patients receiving TAF, and continued treatment through 8 years demonstrated declines consistent with normal aging[11]
- After switching from TDF to TAF, improvements in $eGFR_{CG}$ were observed in patients with and without risk factors showing reversibility in TDF-associated declines
- Among the TDF→TAF groups, a greater recovery in $eGFR_{CG}$ was observed in those with ≥1 TDF risk factor who switched from TDF to TAF after 2 years (TDF→TAF OL6y) vs after 3 years (TDF→TAF OL5y)

Changes in Renal Tubular Markers Over 8 Years Among Patients With ≥1 TDF Risk Factor



β_2M:Cr, β_2-microglobulin to creatinine ratio; OL, open-label; Q, quartile; RBP:Cr, retinol binding protein to creatinine ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Over 8 years of TAF treatment, median % increases in β_2M:Cr and RBP:Cr remained relatively stable
- Among patients with ≥1 TDF risk factor, tubular proteinuria increased during DB TDF treatment and then markedly improved after switching from TDF to TAF