Long term efficacy and safety of NUCs: follow-up studies of TDF and TAF

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Disclosures

Maria Buti, MD, FAASLD, has a financial interest/relationship or affiliation in the form of:

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Advisory Board for AbbVie Inc.; Altimmune, Inc; Assembly Biosciences, Inc.; Gilead Sciences, Inc.; GlaxoSmithKline plc.; and Janssen Inc.

Introduction

Approximately 316 million people worldwide have chronic hepatitis B resulting in over 800,000 deaths in 2019

Nucleos(t)ide analogues suppress viral replication, slow or reverse fibrosis progression, and reduce HCC risk. HBsAg clearance is rarely seen (<5%).

Therefore lifelong treatment is often required, highlighting the need for safe and effective long-term therapies

Tenofovir disoproxil fumarate (TDF) (2008) and Tenofovir Alafenamide (TAF) (2019) and Entecavir are first-line therapy

Characteristics of Tenofovir Disoproxil Fumarate (TDF) and Tenofovir alafenamide (TAF)

	TDF	TAF*
Prodrug	Tenofovir	Tenofovir
Antiviral Efficacy	+++	+++
Dose	Higher	1/10 of TDF
Stability in plasma Circulating levels Hepatic Concentrations	+ Higher Lower	+++ Lower Higher
Dose adjusted to renal function	Yes	No

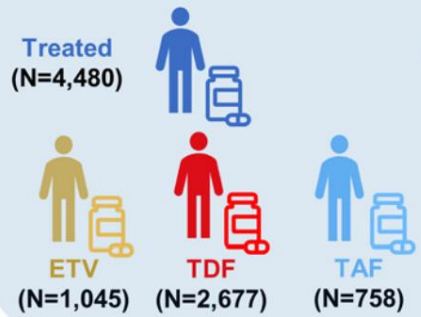
TAF has the potential of better renal and bone safety profile with similar efficacy

1. EASL Guidelines. J Hepatol 2019 **2.** Terraulth N *et al*. Hepatology 2018; **3.** SK *et al*. Hepatol Int. 2016.

Longitudinal Changes in Renal Function in Patients with Chronic Hepatitis B on Antiviral Treatment

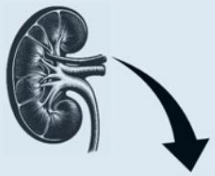
Study population

- Retrospective cohort study
- Patients with chronic hepatitis B (CHB)
- Chronic kidney disease (CKD) stage ≤4 at baseline

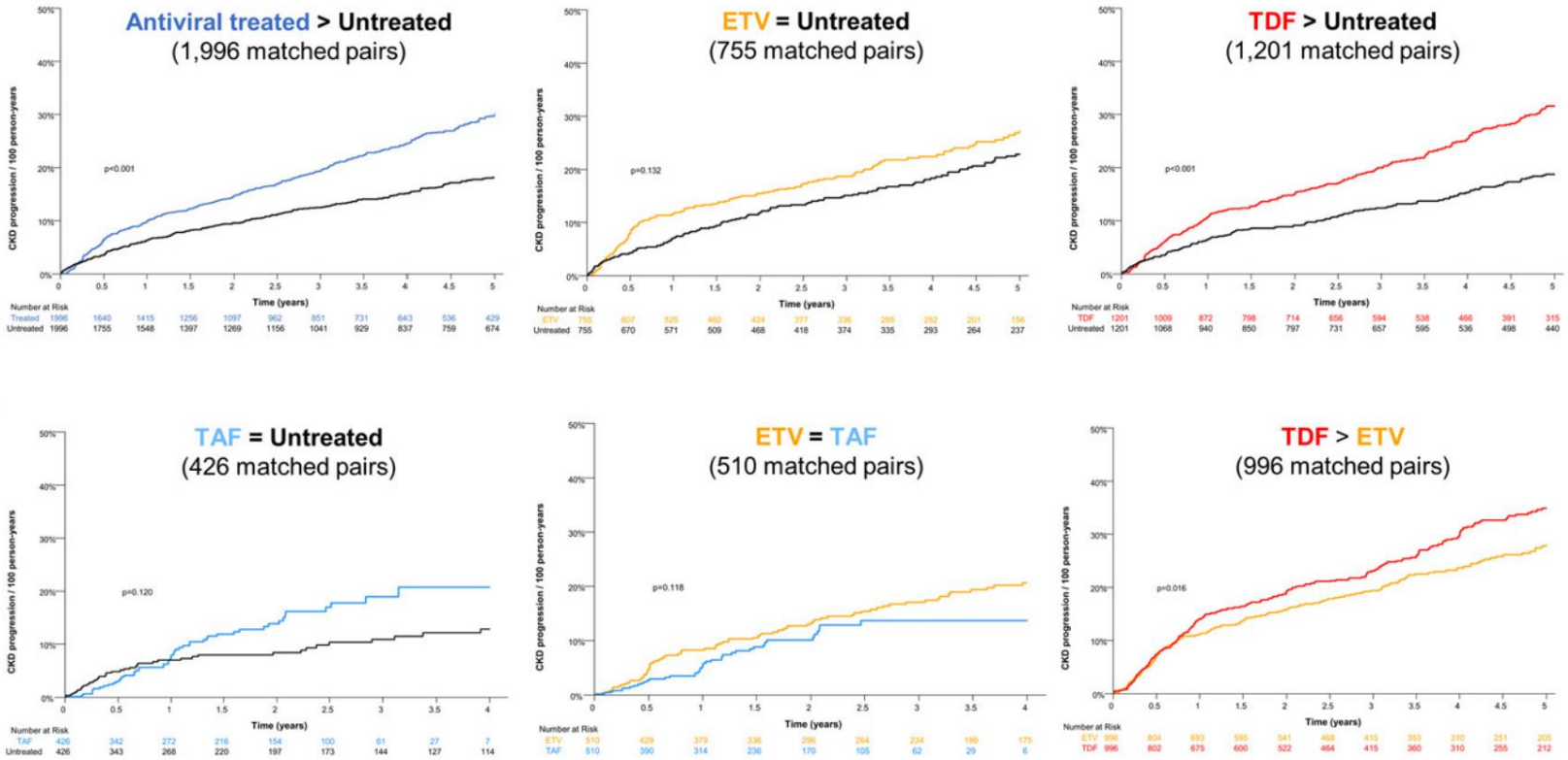


Primary outcome

- Progression of CKD stage ≥1



The cumulative rate of CKD progression



Conclusion

- Antiviral treatment was associated with a significantly increased risk of CKD progression, primarily driven by TDF treatment among patients with CHB
- Both ETV- and TAF-treated patients showed comparable risk of CKD progression when compared with untreated patients

Hong et al. Aliment Pharmacol Ther . 2024 Feb;59(4):515-525

Long-term use of tenofovir disoproxil fumarate increases fracture risk in elderly patients with chronic hepatitis B

Setting & Patients

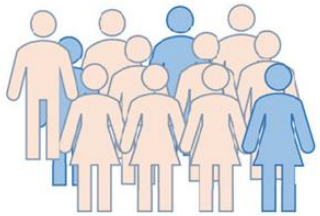
Electronic healthcare database in Hong Kong managed by the Hospital Authority

Coverage of ≈80 % of population

Electronic healthcare database

Systematic data retrieval

Study population and primary endpoint

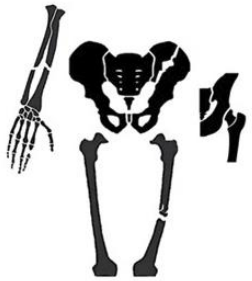


ETV

TDF

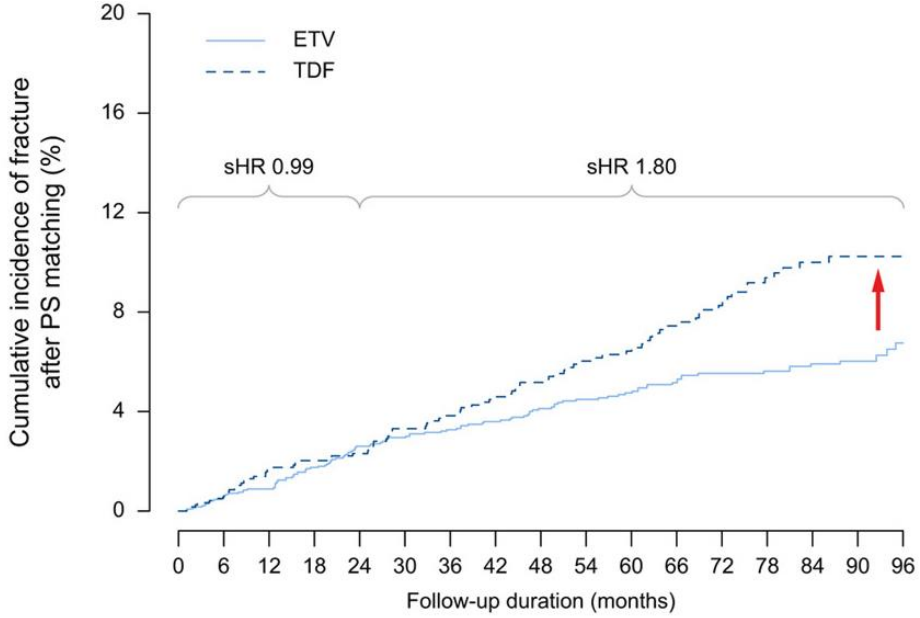
Patients with chronic hepatitis B (CHB) aged ≥60 years between January 2005 and December 2022 receiving ETV or TDF

Propensity score matching



Incident bone fracture

Results



Conclusion:
Fracture risk increased after TDF treatment for ≥24 months in elderly patients with CHB.

Selection of nucleos(t)ide analogues should be individualised based on age and comorbidities.

Yip TC, et al. J Hepatol. 2024 march

Long-Term TAF in CHB Patients over 8 Years

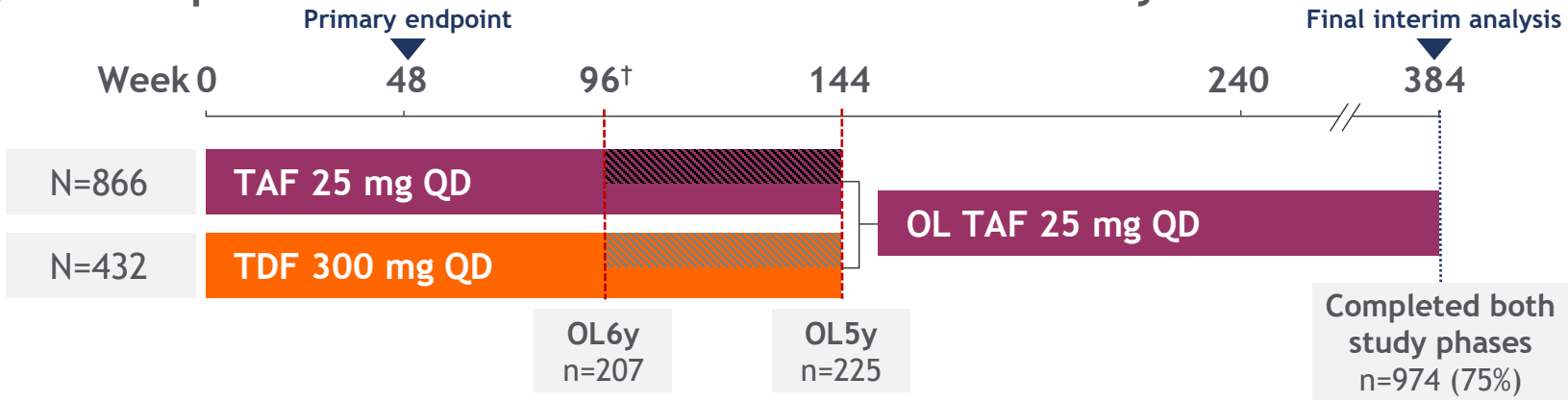
Two phase 3 studies of 1,298 CHB patients treated with TAF or TDF→TAF over 8 years

Studies: 108 (HBeAg-) and 110 (HBeAg+)

Randomization 2:1 (TAF:TDF)

Key inclusion criteria*

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



Key Outcomes

Safety

- Changes in bone and renal parameters
- Cumulative HCC incidence and HCC risk

Viral and Biochemical Efficacy

- HBV DNA <29 IU/mL at Year 8
- ALT normalization by 2018 AASLD and central laboratory criteria

Resistance

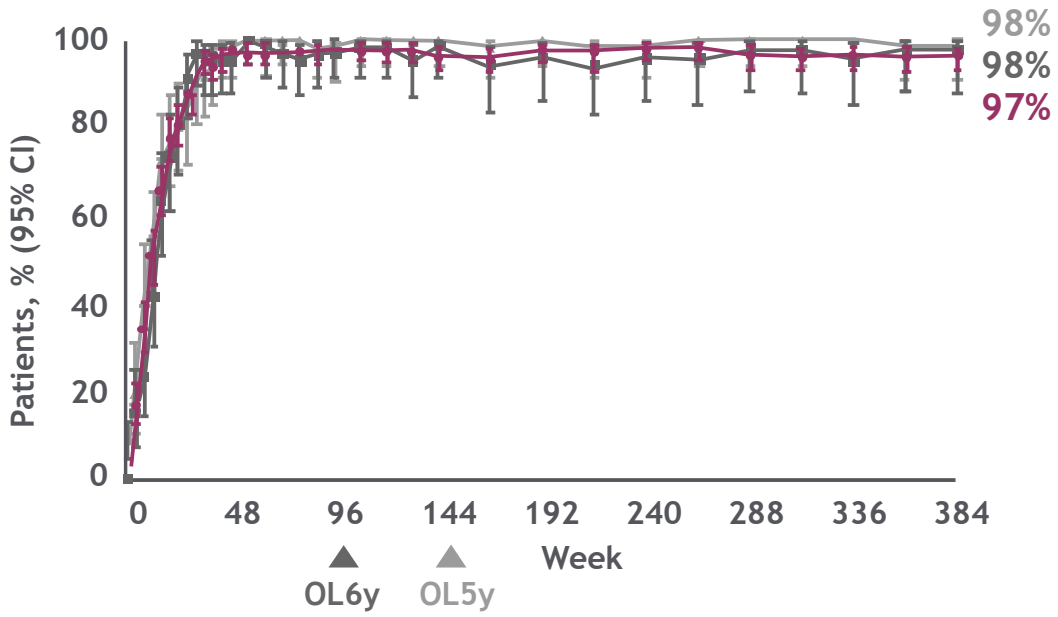
- Deep sequencing of HBV pol/RT for virologic blip, virologic breakthrough, persistent viremia, or discontinuation with viremia (HBV DNA ≥69 IU/mL)

*Double-blind phase: stratified by HBV DNA level and treatment status (naïve/experienced); †Shaded areas represent patients who rolled over to OL TAF at Week 96 (OL6y) or Week 144 (OL5y). AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CHB, chronic hepatitis B; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg+, hepatitis B 'e' antigen-positive; HBeAg-, hepatitis B 'e' antigen-negative; HCC, hepatocellular carcinoma; OL, open-label; pol, polymerase; QD, once daily; RT, reverse transcriptase; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; y, year.

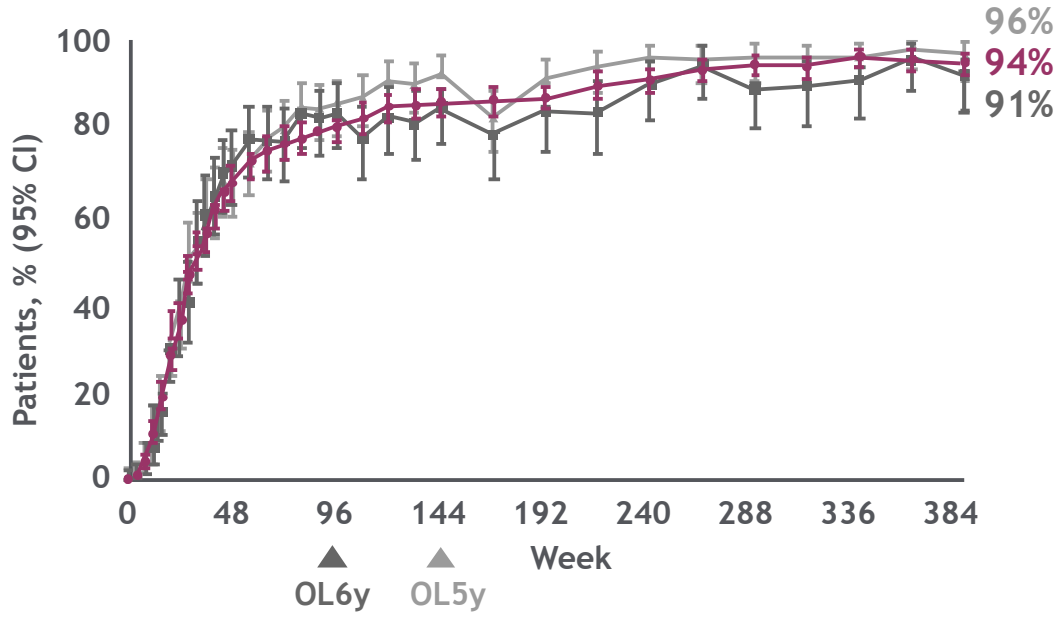
Buti M, et al. AASLD 2023. Poster #1405-C; Lim YS, et al. AASLD 2023. Poster #1422-C; Chan HLY, et al. AASLD 2023. Poster #1430-C

Viral Suppression over 8 Years*,†

Study 108 (HBeAg-)



Study 110 (HBeAg+)



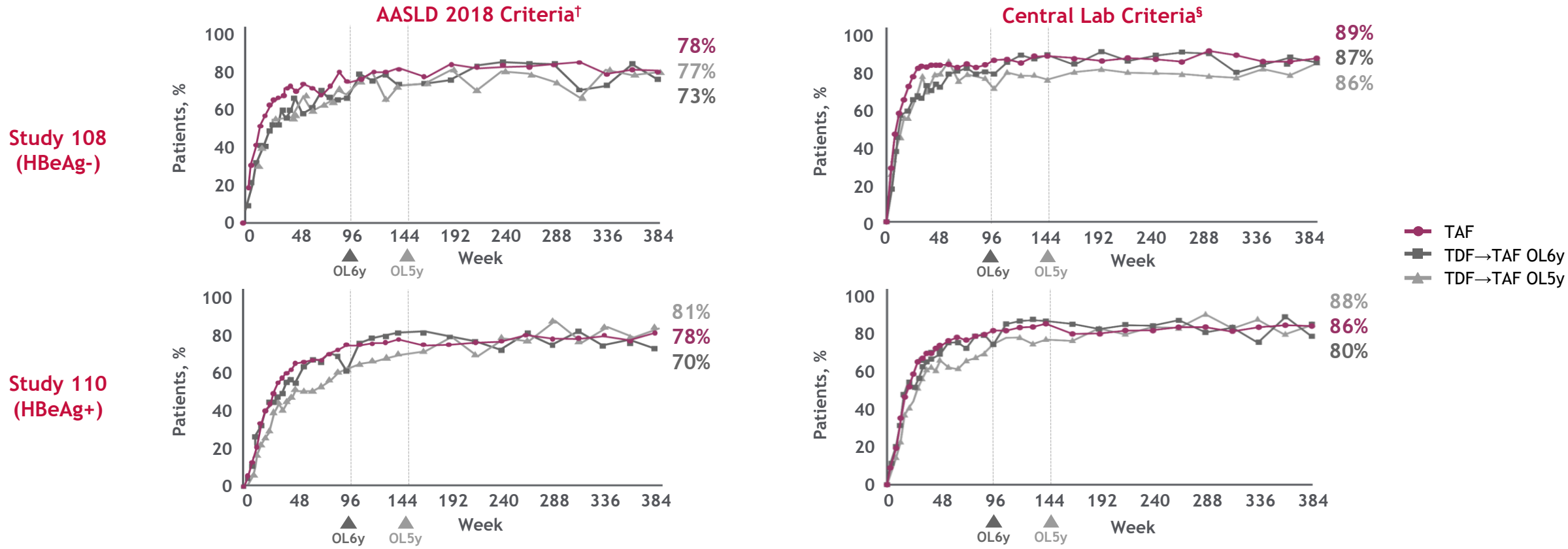
TAF TDF→TAF OL6y TDF→TAF OL5y

High rates of viral suppression achieved and maintained over 8 years

*Missing = excluded analysis; †HBV DNA <29 IU/mL at year 8. CHB, chronic hepatitis B; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

Buti M, et al. EASL 2023. Oral #OS-067

ALT Normalization over 8 Years*



High rates of ALT normalization with continuous TAF and increased rates occurred after TDF→TAF switch

*Missing = excluded analysis; †Men ≤35 U/L and women ≤25 U/L; §Men ≤43 U/L and women ≤34 U/L (≥69 y: men ≤35 U/L and women ≤32 U/L). CHB, chronic hepatitis B; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.

Buti M, et al. EASL 2023. Oral #OS-067

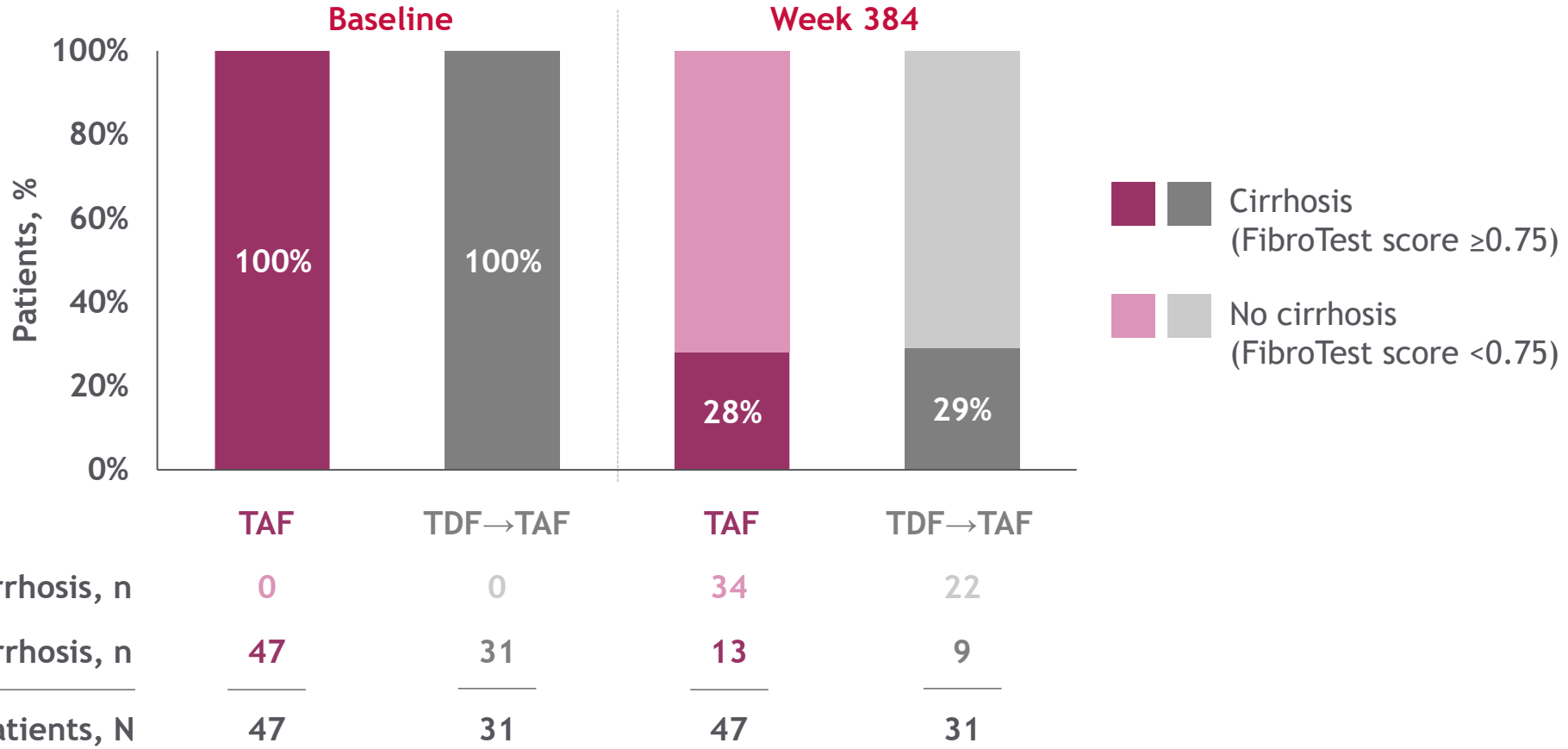
HBsAg and HBeAg Loss and Seroconversion at Year 8

HBsAg	TAF		TDF→TAF OL6y		TDF→TAF OL5y	
	HBeAg negative	**HBeAg positive**	**HBeAg negative**	**HBeAg positive**	**HBeAg negative**	**HBeAg positive**
Loss, n/n (%)	8/199 (4)	9/384 (2)	0/41	4/76 (5)	1/58 (2)	3/109 (3)
Seroconversion, n/n (%)	6/199 (3)	6/384 (2)	0/41	4/76 (5)	0/58	3/109 (3)
Mean $\log_{10}$ IU/mL change (SD)	n = 208 –0.62 (0.924)	n = 393 –0.89 (1.211)	n = 44 –0.50 (0.526)	n = 81 –1.09 (1.424)	n = 58 –0.61 (0.758)	n = 112 –1.09 (1.268)
HBeAg loss/seroconversion		49%/33%		46%/31%		44%/27%

— Low rates of HBsAg loss (≤5%) and small mean declines in qHBsAg were seen at year 8

— No TAF resistance detected through Year 8 of treatment in adults with CHB

Regression of Cirrhosis by FibroTest over 8 Years*,†



	TAF	TDF→TAF	TAF	TDF→TAF
Patients without cirrhosis, n	0	0	34	22
Patients with cirrhosis, n	47	31	13	9
Total patients, N	47	31	47	31

Most patients with cirrhosis at baseline showed improvement

*Missing = excluded analysis; †Pooled analysis of studies 108 (HBeAg-) and 110 (HBeAg+). CHB, chronic hepatitis B; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Buti M, et al. EASL 2023. Oral #OS-067

Open-Label Safety Outcomes

Adverse Events*

Patients, n (%)	TAF (n=775)	TDF→TAF (n=382)
Any AE	525 (68)	271 (71)
Grade 3 or 4 AE	60 (8)	27 (7)
Grade 3 or 4 AE related to study drug	2 (<1)	0
Serious AE	97 (13)	49 (13)
Serious AE related to study drug	4 (1)	0
Discontinuation due to AE	9 (1)	3 (1)
Death†	1 (<1)	0
HCC§	8 (1)	6 (2)

<1% (n=11) of patients discontinued OL TAF treatment due to an AE

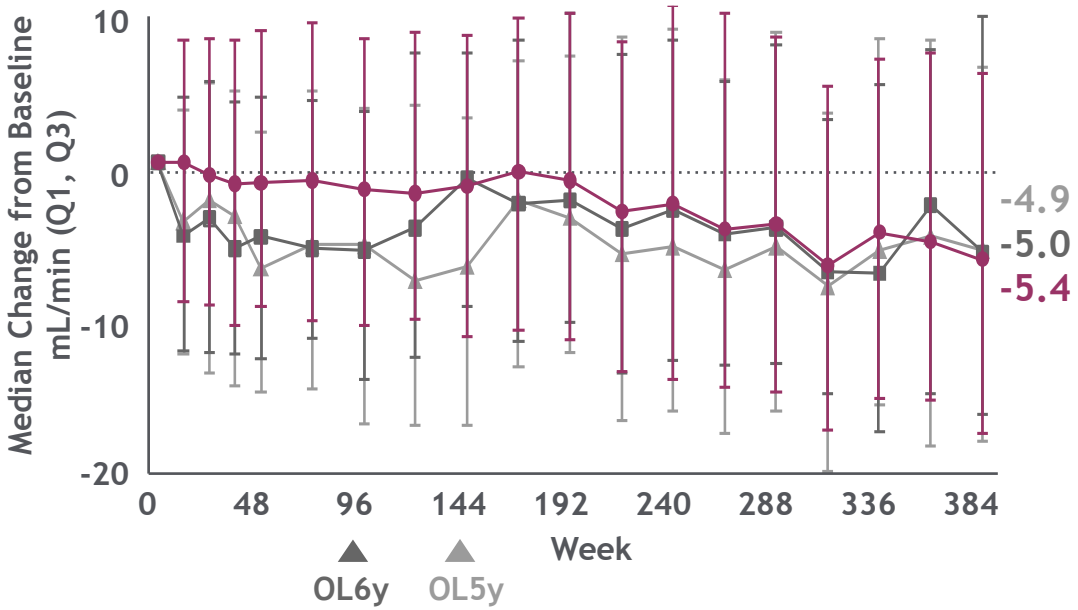
Continuous TAF and TDF→TAF switch resulted in few Grade 3 or 4 AEs and serious AEs

*Among patients in OL safety analysis who received ≥1 dose of OL study drug; †Treatment-emergent death (6 total deaths in the study); §14 HCC occurred during OL phase; 21 HCC cases occurred during DB and OL phases. AE, adverse event; CHB, chronic hepatitis B; DB, double-blind; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; HCC, hepatocellular carcinoma; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

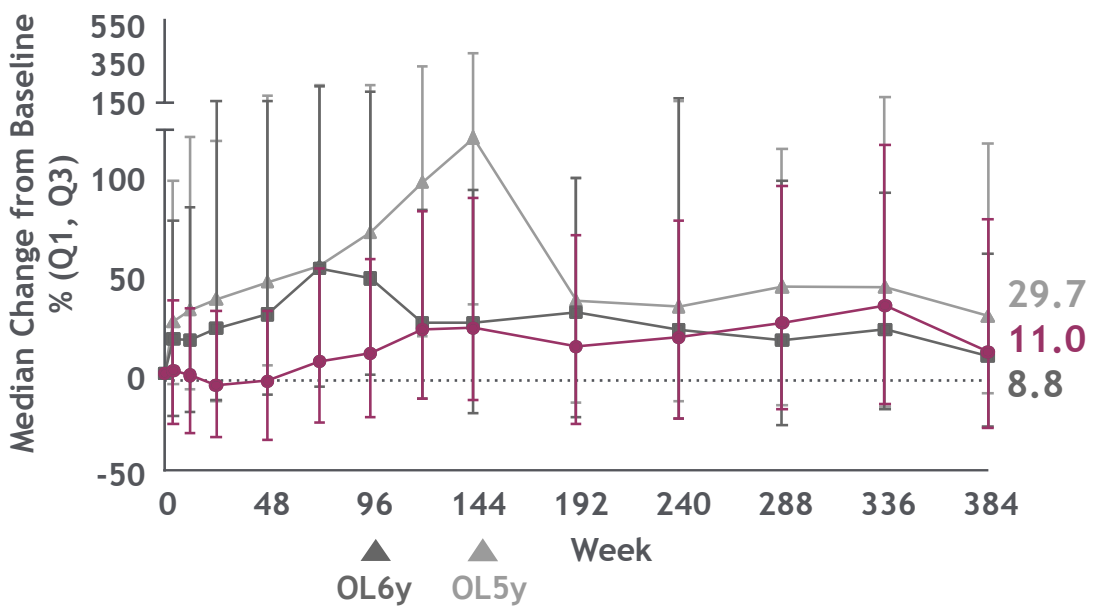
Lim YS, et al. EASL 2023. Poster #SAT-153

Renal Safety over 8 Years

$eGFR_{CG}$



β_2M:Cr



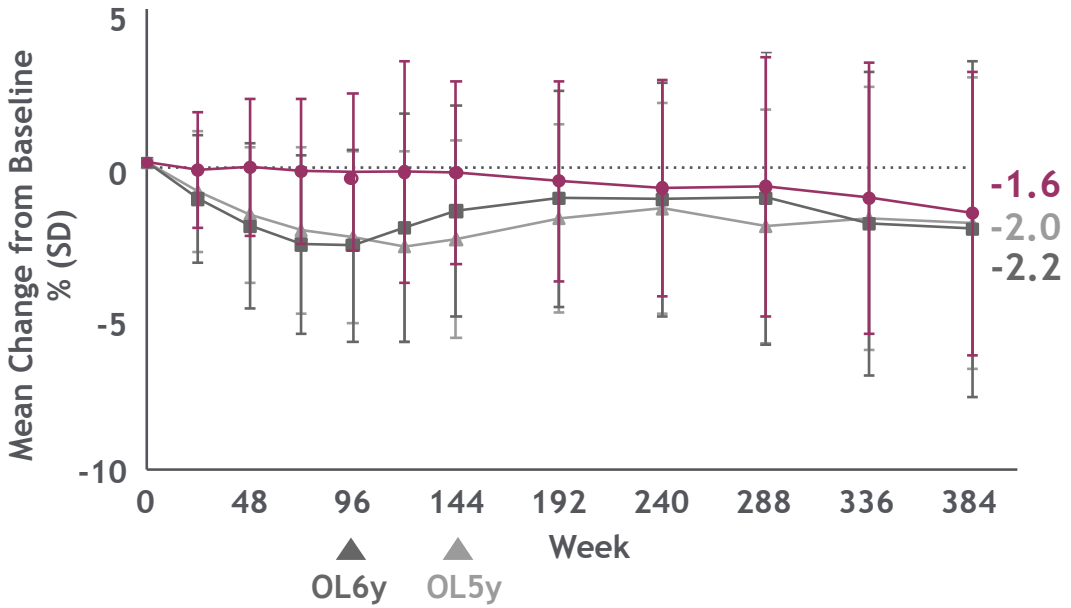
TAF | TDF→TAF OL6y | TDF→TAF OL5y

Continuous TAF resulted in declines in $eGFR_{CG}$[1] that were consistent with aging; TDF-associated declines in renal function were reversed after TDF→TAF switch

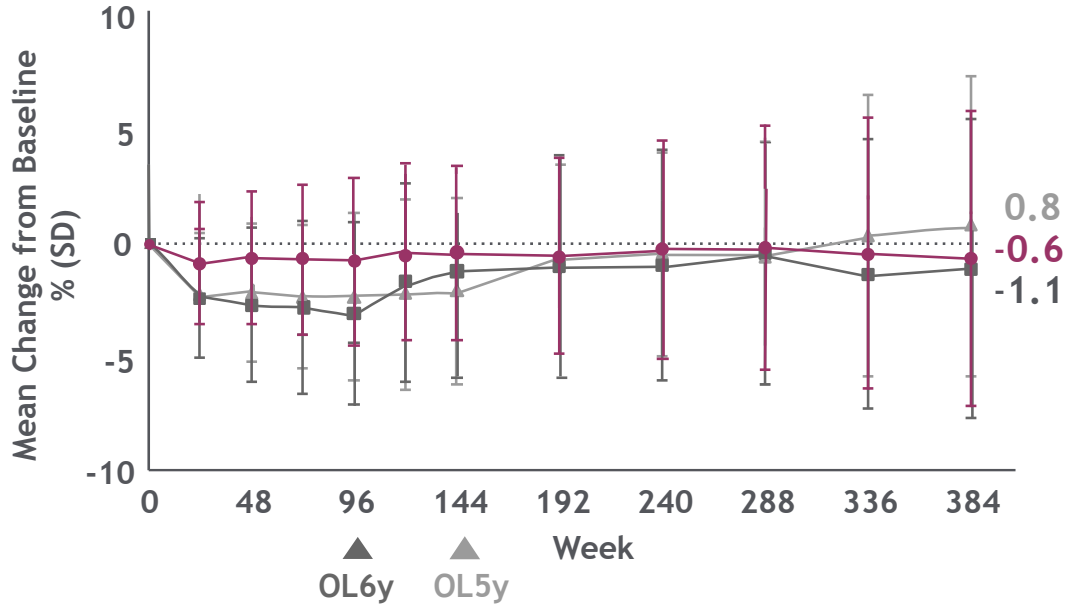
13 β_2M:Cr, β_2-microglobulin to creatinine ratio; CHB, chronic hepatitis B; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; OL, open label; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.
Lim YS, et al. EASL 2023. Poster #SAT-153

Bone Safety over 8 Years

Hip BMD



Spine BMD



TAF TDF→TAF OL6y TDF→TAF OL5y

Continuous TAF resulted in minimal declines in hip and spine BMD*;
TDF-induced bone loss is reversible after TDF→TAF switch

*Declines are consistent with normal aging.[1] BMD, bone mineral density; CHB, chronic hepatitis B; HBeAg+, hepatitis B e antigen-positive; HBeAg-, hepatitis B e antigen-negative; OL, open label; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; y, year.
Lim YS, et al. EASL 2023. Poster #SAT-153

Baseline Characteristics – TAF 8-Year Sub-Analysis

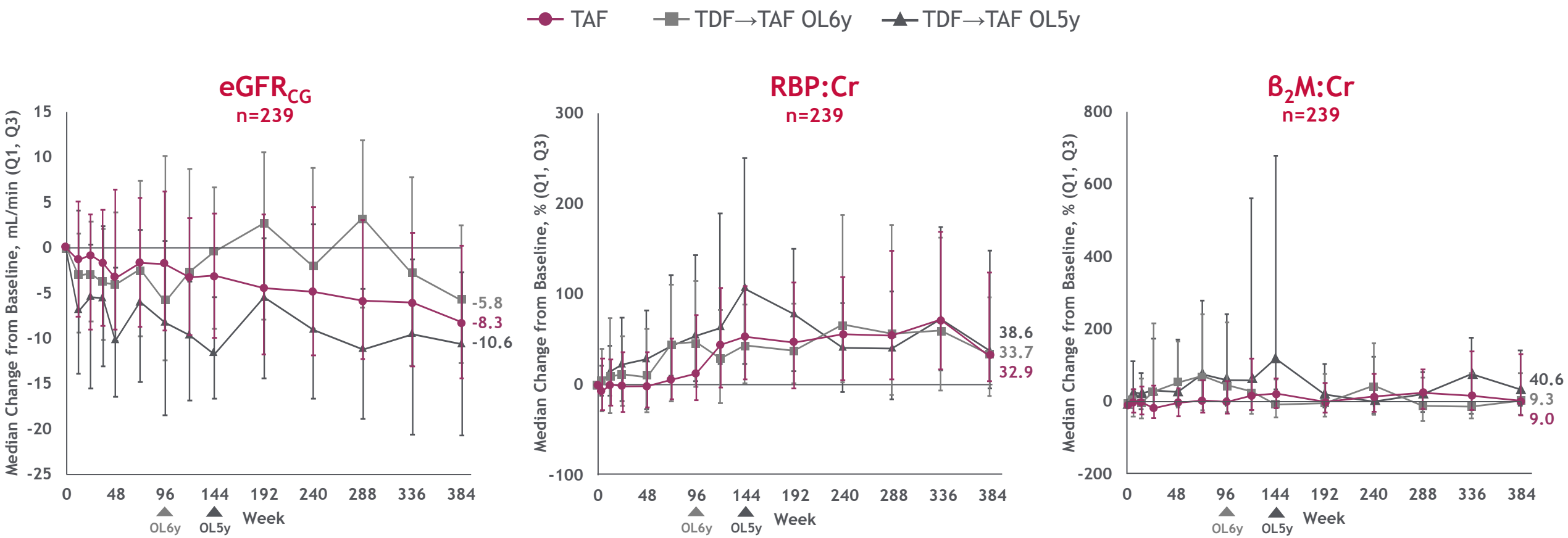
Parameter	All Patients		Patients with ≥1 Risk Factor for TDF	
	TAF n=866	TDF→TAF n=432	TAF n=151	TDF→TAF n=88
Age, years, mean (range)	40 (18–80)	41 (18–72)	48 (20–80)	49 (25–72)
Male, n (%)	544 (63)	275 (64)	91 (60)	53 (60)
Asian, n (%)	687 (79)	333 (77)	122 (81)	70 (80)
HBeAg–, n (%)	297 (36)	142 (33)	73 (48)	40 (46)
FibroTest score ≥0.75, n/n (%)	76/866 (9)	42/432 (10)	26/145 (18)	14/87 (16)
Nucleos(t)ide experienced, n (%)	211 (24)	108 (25)	37 (25)	20 (23)
$eGFR_{CG}$ mL/min, median (Q1, Q3)	106 (91, 125)	105 (90, 124)	95 (91, 113)	98 (81, 118)
Age >60 years, n (%)	42 (5)	28 (6)	42 (28)	28 (32)
Osteoporosis of hip/spine, n (%)	60 (7)	30 (7)	60 (40)	30 (34)
$eGFR_{CG}$ <60 mL/min, n (%)	5 (<1)	4 (<1)	5 (3)	4 (5)
UACR >30 mg/g, n (%)	44 (5)	28 (6)	44 (29)	28 (32)
Serum phosphate <2.5 mg/dL, n (%)	19 (2)	12 (3)	19 (13)	12 (14)

Baseline risk factors for renal and bone toxicities with TDF*

*Based on 2017 EASL guidelines. EASL, European Association for the Study of the Liver; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; HBeAg, hepatitis B 'e' antigen; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UACR, ratio of urine albumin to creatinine.

Buti M, et al. AASLD 2023. Poster #1405-C

Renal Safety in Adults with TDF Risk Factors*

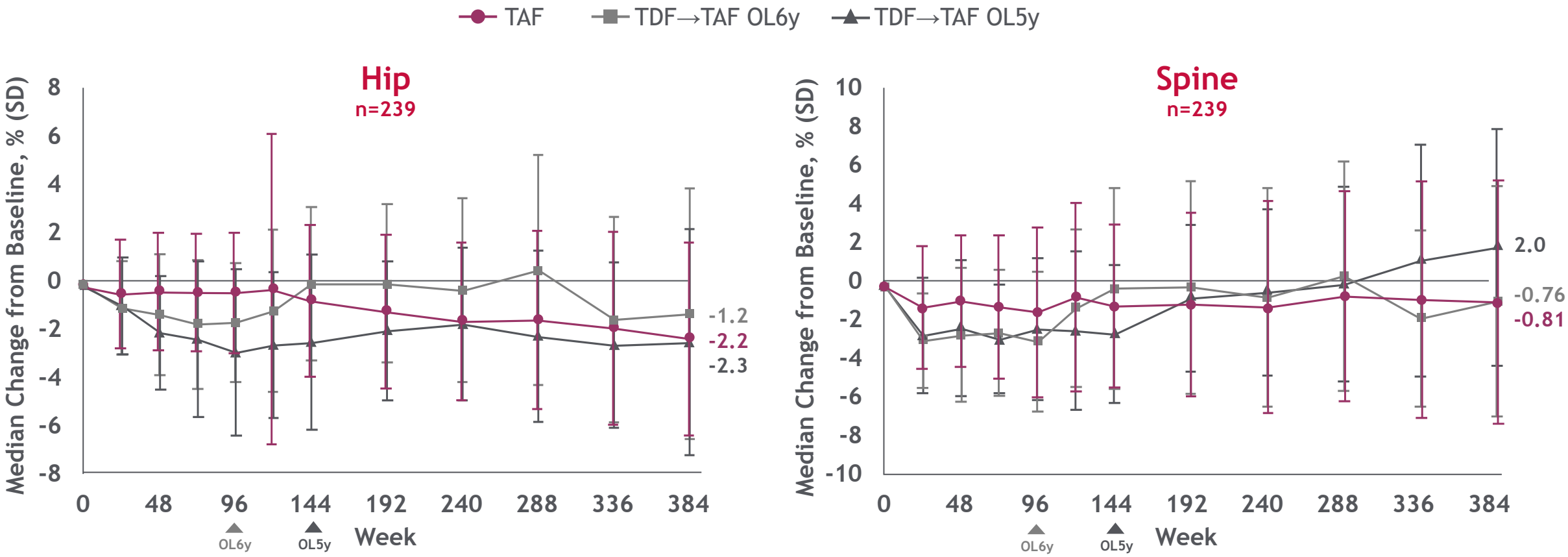


eGFR$_{CG}$ decline with continuous TAF consistent with normal aging;[1] renal parameters improved with TDF→TAF switch

*Based on 2017 EASL guidelines. Risk factors for renal and bone toxicities with TDF: age >60 years; osteoporosis; eGFR$_{CG}$ <60 mL/min; ratio of urine albumin to creatinine >30 mg/g; serum phosphorous <2.5 mg/dL. β$_2$M:Cr, β$_2$-microglobulin to creatinine ratio; EASL, European Association for the Study of the Liver; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; OL, open-label; Q1, first quartile; Q3, third quartile; RBP:Cr, retinol binding protein to creatinine ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Buti M, et al. AASLD 2023. Poster #1405-C

Bone Safety in Adults with TDF Risk Factors*



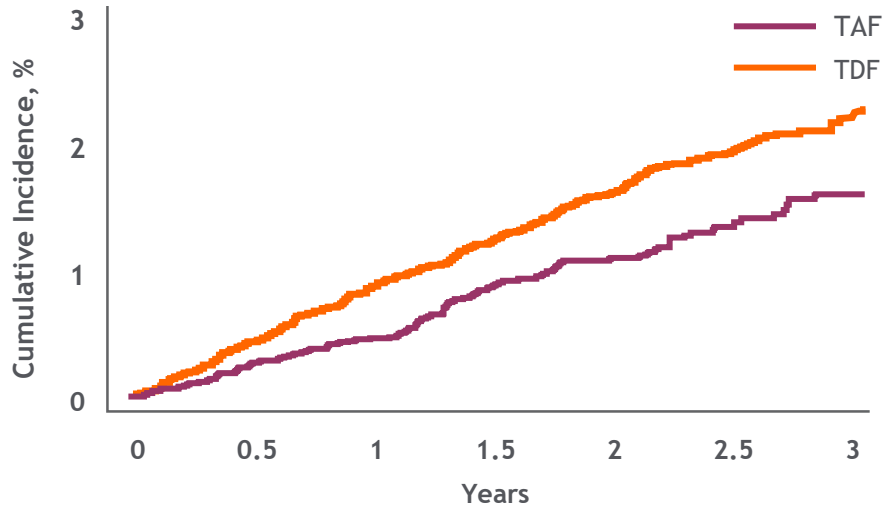
*Based on 2017 EASL guidelines. Risk factors for renal and bone toxicities with TDF: age >60 years; osteoporosis; $eGFR_{CG}$ <60 mL/min; ratio of urine albumin to creatinine >30 mg/g; serum phosphorous <2.5 mg/dL. BMD, bone mineral density; EASL, European Association for the Study of the Liver; OL, open-label; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Buti M, et al. AASLD 2023. Poster #1405-C

Risk of Osteoporotic Fracture in TDF- vs. TAF-Treated CHB Patients

Retrospective claims study of 32,582 CHB patients from 2017-2020

Fracture Incidence*



Fracture Incidence			
TAF n=11,705	111 events (0.5/100 PY)	HR† (95% CI) 0.7 (0.6-0.9) p=0.001
TDF n=20,977	339 events (0.8/100 PY)	

Fracture Incidence by Baseline Variables†

Variable	TAF n=11,705	TDF n=20,877	HR (IPTW) 95% CI	p value
Sex				
Male	0.4 (0.3–0.6)	0.8 (0.7–0.9)	0.6 (0.5–0.8)	0.002
Female	0.6 (0.4–0.8)	0.8 (0.7–1.0)	0.8 (0.6–1.1)	0.149
Age group				
18–49	0.3 (0.2–0.4)	0.4 (0.3–0.5)	0.7 (0.5–1.1)	0.12
50–99	0.8 (0.6–1.0)	1.3 (1.1–1.4)	0.6 (0.5–0.8)	0.001
Cirrhosis				
Yes	0.7 (0.5–0.9)	1.1 (0.9–1.3)	0.7 (0.5–0.9)	0.018
No	0.4 (0.3–0.5)	0.7 (0.6–0.8)	0.7 (0.5–0.9)	0.013

TAF was associated with significantly lower risk of osteoporotic fracture than TDF

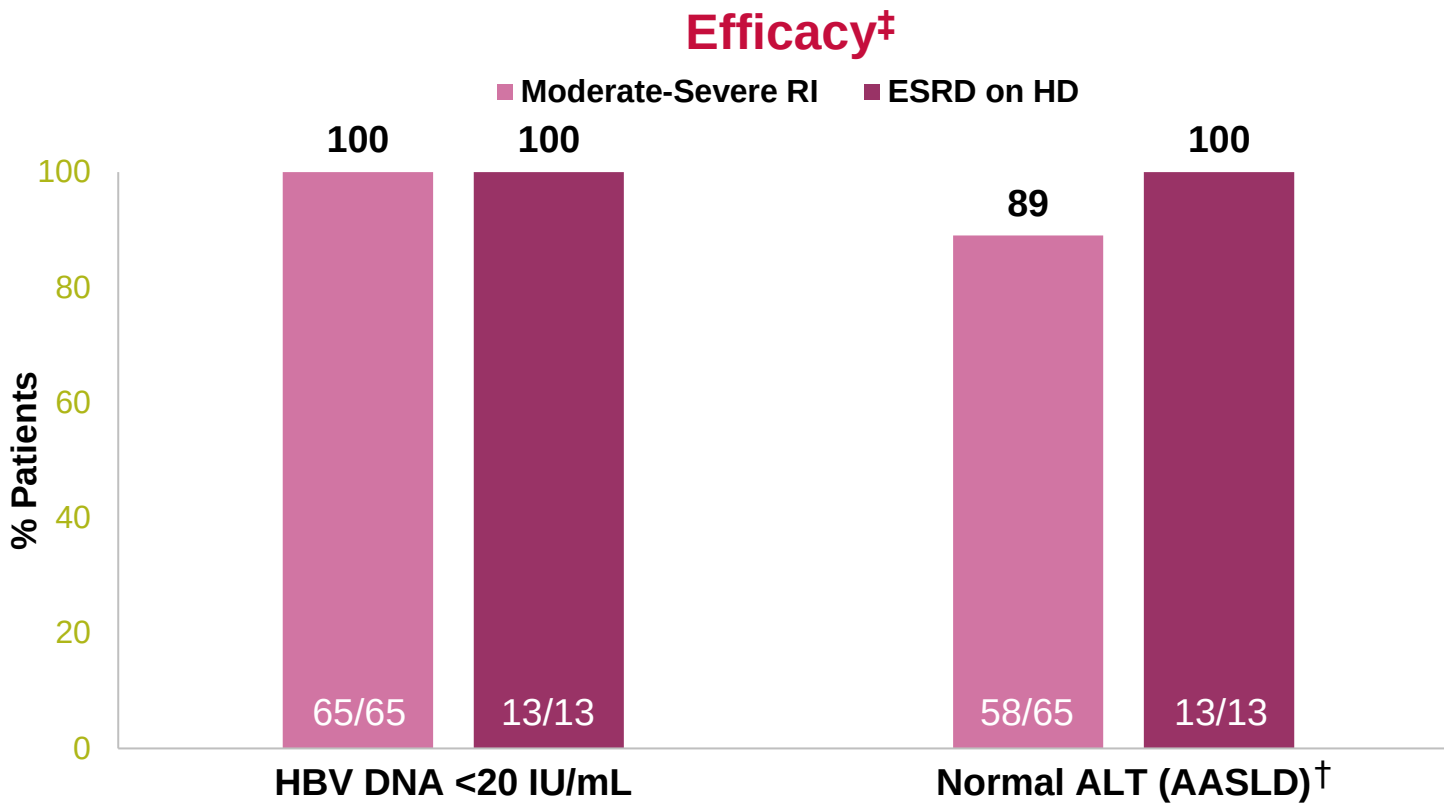
*After IPTW. †Baseline characteristics were well-balanced after IPTW adjustment. CHB, chronic hepatitis B; CI, confidence interval; HR, hazard ratio; IPTW, Inverse probability of treatment weighting; NR, not reported; PY, person-year; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Kim E, et al. EASL 2023. #SAT-146

Renal Impairment Cohort: Baseline Characteristics & Efficacy

Open-label study of switching to TAF in 93 patients with moderate-severe renal impairment or ESRD

Baseline Characteristics	Moderate-Severe RI n=78	ESRD on HD n=15
Median age, years (range)	67 (39-85)	57 (32-72)
Female, n (%)	21 (27)	3 (20)
Asian, n (%)	59 (76)	13 (87)
HBeAg-negative, n (%)	65 (83)	12 (80)
HBV DNA <20 IU/mL, n (%)	77 (99)	14 (93)
ALT ≤ULN (AASLD), n (%)	73 (94)	15 (100)
Median $eGFR_{CG}$, mL/min (Q1, Q3)	46 (36, 55)	7 (6, 10)
Hip T-score ≤-2.5, n (%)	7 (9)	7 (47)
Spine T-score ≤-2.5, n (%)	19 (24)	3 (20)
TDF at screening*	56 (72)	1 (7)
ETV at screening*	18 (23)	10 (67)



Renally-impaired CHB patients who were switched to TAF maintained high rates of viral suppression, with a high rate of normal ALT at Week 96

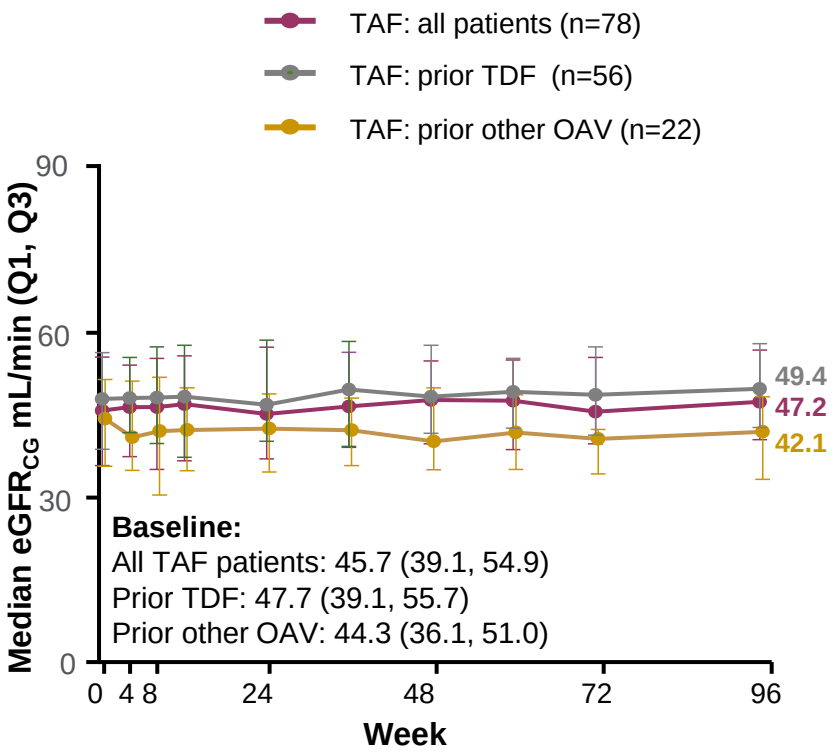
‡ Missing = excluded analysis. * Patients could have taken >1 agent previously. †Normal ALT defined as ALT < ULN at week 96 regardless of baseline ALT level. ESRD, end-stage renal disease; HD, hemodialysis; RI, renal impairment. Virally suppressed patients = HBV DNA <LLOQ x 6 months and <20 IU/mL at screening. Moderate to severe renal impairment = $eGFR_{CG}$ 15 - <60 mL/min at screening. ESRD on HD: $eGFR_{CG}$ < 15 mL/min maintained on chronic hemodialysis. AASLD 2018 criteria defined as ALT 25 U/L for women and 35 U/L for men

Janssen HLA, et al. EASL 2021. #2395

Renal Impairment Cohort: Renal and Bone Parameters

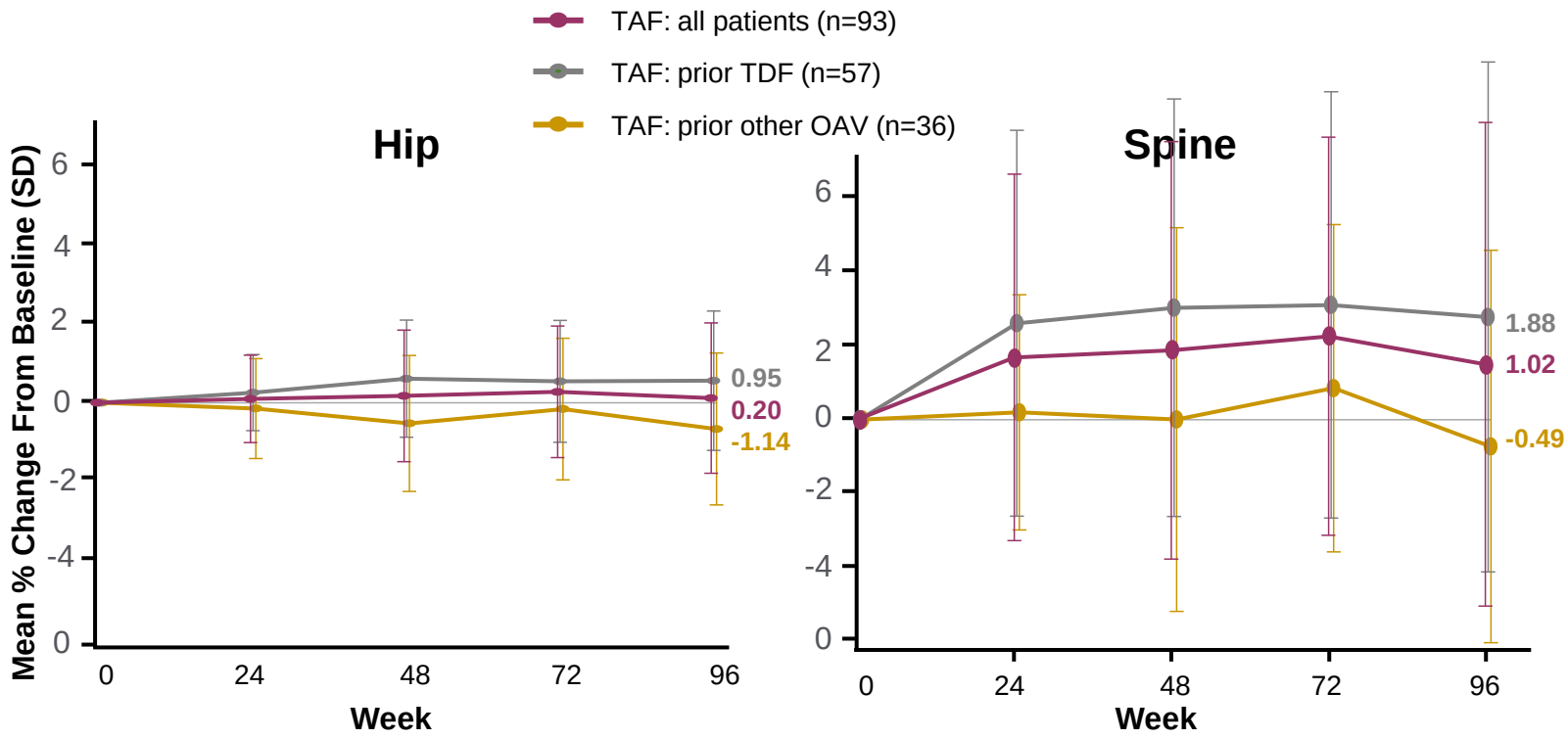
Changes in Creatinine Clearance

Moderate-Severe RI



Changes in BMD

Moderate–Severe RI + ESRD



In renally impaired CHB patients, including those with ESRD on hemodialysis, switching from TDF and/or other oral antivirals to TAF maintained stable renal and bone function

BMD, bone mineral density; ESRD, end stage renal disease; OAV, oral antiviral; RI, renal impairment.
Janssen HLA, et al. EASL 2021. #2395

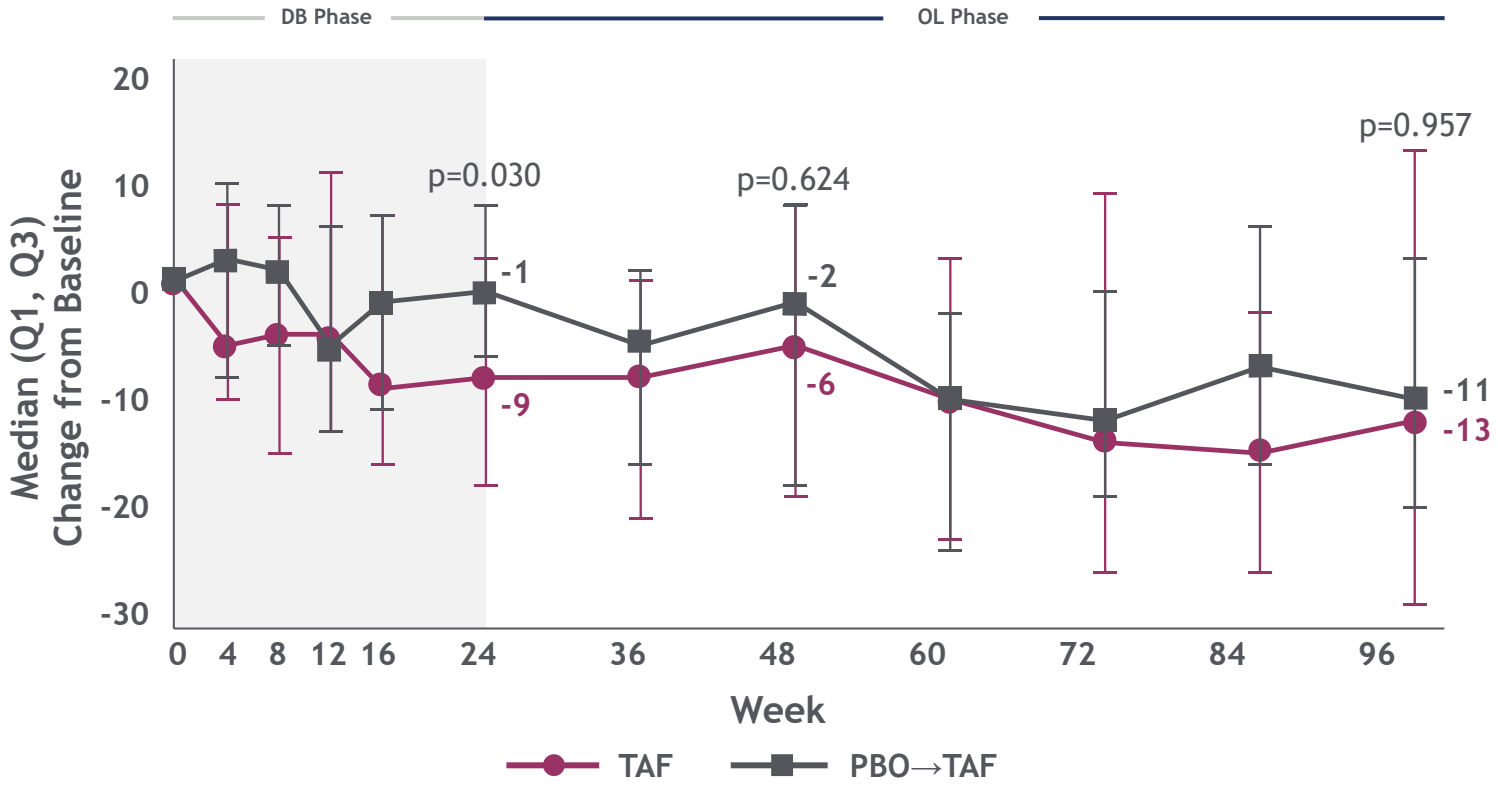
GS-US-320-1092

Overall and Renal Safety of TAF in Children and Adolescents with CHB (≥6 and <18y, ≥35 kg

AEs and Laboratory Abnormalities*

Patient, n (%)	TAF n=59	PBO→TAF n=29
Any AE	41 (70)	22 (76)
Any study drug-related AE	12 (20)	4 (14)
Grade 3 or 4 AE	3 (5)¶	3 (3)
Serious AE	1 (2)†	0
Discontinued due to AE	0	0
Grade 3 or 4 laboratory abnormalities	13 (22)	5 (17)

Change in Creatinine Clearance§



TAF was well-tolerated; creatinine clearance changes were similar for PBO →TAF and continuous TAF

*Open-label phase; ¶Grade 3 AEs: mononucleosis, tibia fracture; Grade 4 AE: suicidal ideation; †Non-treatment-related suicidal ideation; §Continuous baseline value data expressed as median (Q1, Q3) and based on the Schwartz formula. P values were based on a 2-sided Wilcoxon rank sum test. AE, adverse event; ALT, alanine aminotransferase; CHB, chronic hepatitis B; DB, double-blind; OL, open-label; PBO, placebo; Q1, first quartile; Q3, third quartile; TAF, tenofovir alafenamide.

Schwarz KB, et al. AASLD 2023. Poster #1414-C

Bone Safety of TAF in Children and Adolescents with CHB

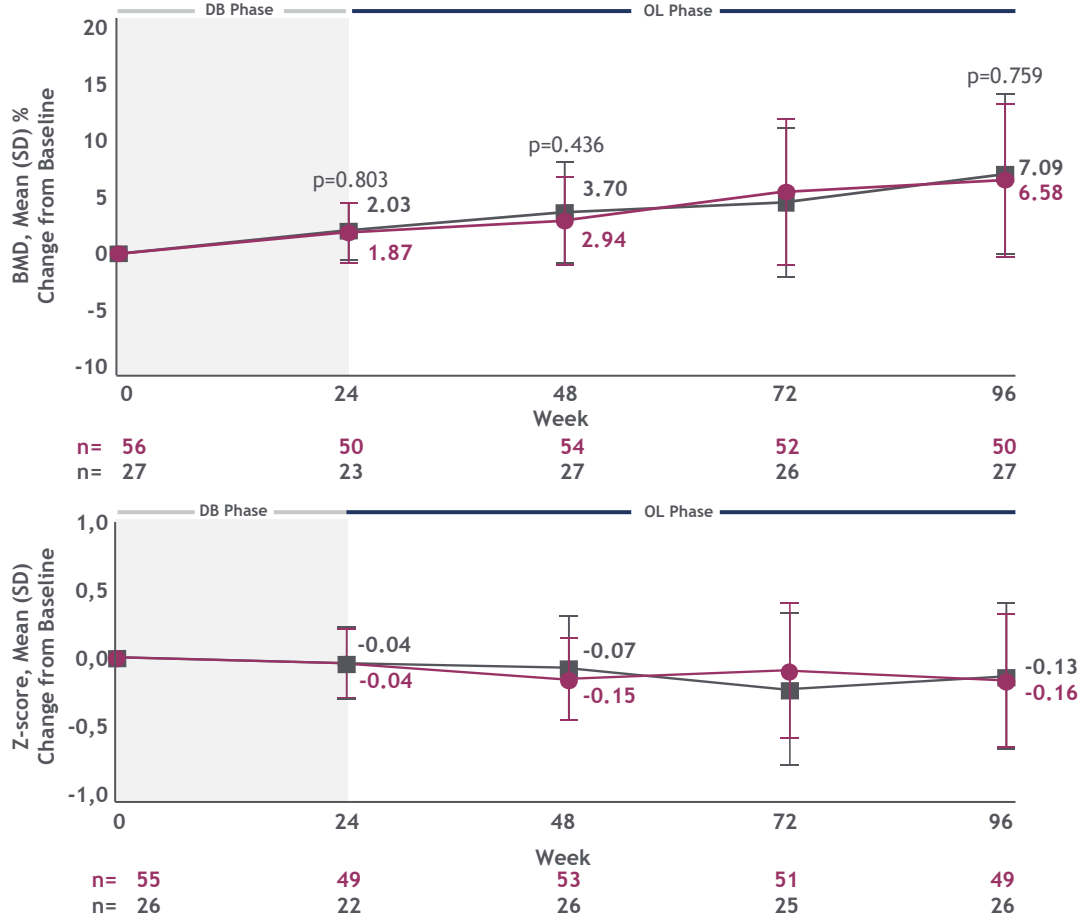
BMD*

Z-Score*

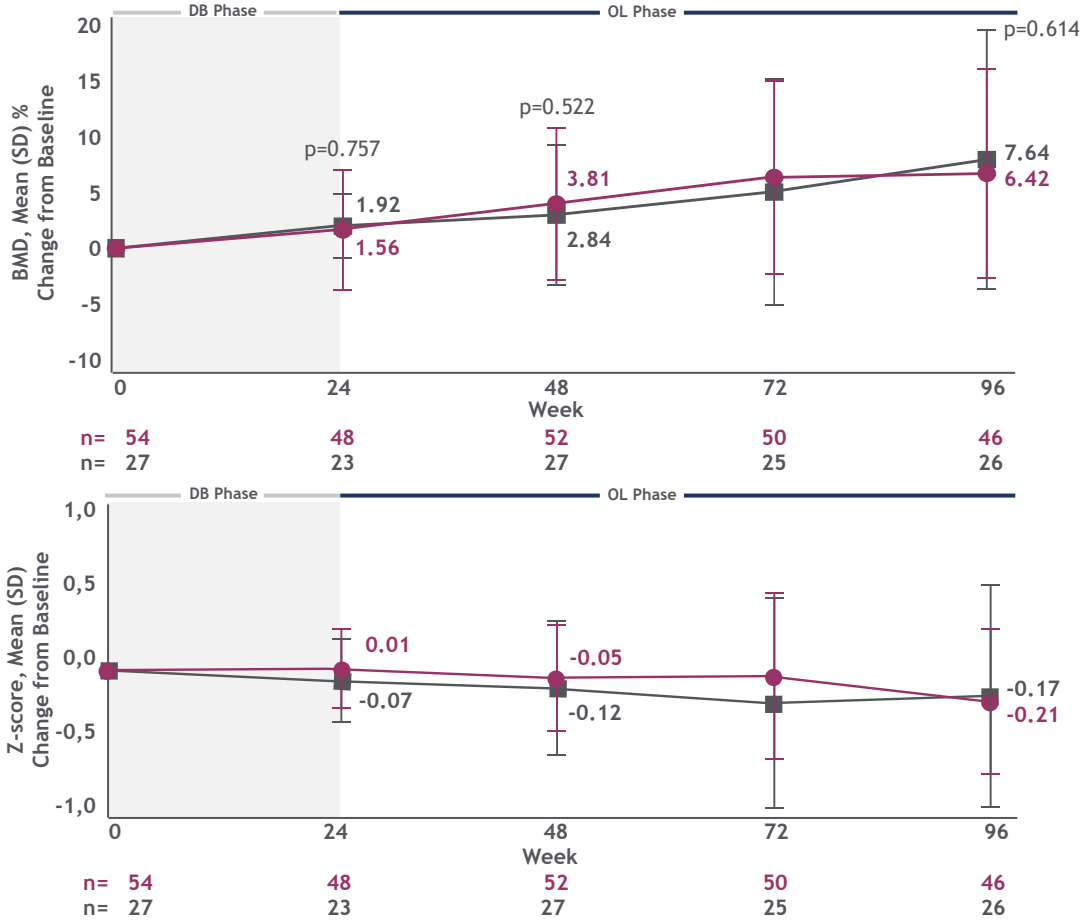
TAF

PBO→TAF

Whole Body



Spine



BMD and Z-score changes were similar for PBO→TAF and continuous TAF

*P values were based on an ANOVA model, including treatment as a fixed effect. ANOVA, analysis of variance; BMD, bone mineral density; CHB, chronic hepatitis B; DB, double-blind; OL: open-label; PBO, placebo; SD, standard deviation; TAF, tenofovir alafenamide.

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Conclusions

Long-term treatment with TAF In patients with chronic HBV is associated with

High rates of persistent viral suppression (91%–98%), normal ALT and improvement of fibrosis

Infrequent HBsAg loss

No resistance

TAF is associated with continuous declines in eGFR and minimal declines in hip and spine BMD; that were consistent with aging

- TAF in renally impaired CHB patients, including those with ESRD on hemodialysis, maintained stable renal and bone function
- TAF in Children and Adolescents is safe and well tolerated

These results provide continued support for TAF over TDF as the preferred treatment for chronic HBV infection